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ORIGINAL ARTICLE

Are chronic urticaria, analgesic intolerance and seasonal rhinitis markers of different severities and phenotypes of the asthma they accompany?

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Abstract
Background: Asthma is a heterogeneous disease that presents with different clinical phenotypes. We aimed to compare the patients with asthma diagnosis alone with the patients, who, in addition to their asthma had accompanying analgesic intolerance (AI), chronic urticaria (CU) or seasonal rhinitis (SR) if there are any distinctions and specific characteristics of these defined patient groups.
Methods: Eighty-four asthma patients diagnosed with SR, 46 with CU, 75 with AI and 71 patients with asthma alone were enrolled to the study retrospectively. The reference group for the comparisons was the group with astma diagnosis alone.
Results: The mean age of all patients was 37.2 ± 13 (15–80) and 70.7% of them were females. Asthma patients with SR had a significantly earlier onset of asthma (age: 27.4 ± 10.8 and 34.5 ± 15.9; respectively, $p < 0.01$), significantly better pulmonary function tests and were significantly more atopic (92.9% and 28.8%; $p < 0.001$). Moderate-to-severe asthma significantly correlated with older age at the time of diagnosis, older age of asthma onset, higher body mass index, less atopy and fewer pollen sensitivity. Asthma severity of patients with SR was significantly milder than the reference group (OR: 0.6, 95% CI 0.5–0.8). Asthma with AI tended to be more severe although the relation was insignificant (OR:1.6 95% CI:0.8–3.5).
Conclusions: Asthma patients with SR have significantly milder and earlier onset of asthma, better pulmonary function tests and are significantly more atopic while asthma with AI tends to be more severe. Asthma with CU does not show a specific phenotypic characteristic.
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Introduction

Asthma is the most frequently seen pulmonary disease which affects nearly 300 million individuals worldwide.[1] Although various treatment guidelines have provided consensus definitions of asthma, these definitions could not possibly reflect the differences in clinical manifestations of the disease.[1,2] It seems to be a heterogeneous disease which presents with different clinical phenotypes.

Phenotype is described as ''all the observable characteristics of an organism that result from the interaction of its genotype and the environment''.[3] Although different phenotypes of asthma have drawn the attention of clinicians for many years, most of them have been gathered under the classical term ''asthma'' since biomarkers, genetic or physiopathological characteristics of these phenotypes have not been adequately and effectively defined. However, in recent years, the idea of phenotype specific treatment has led to more detailed phenotyping attempts.[4]

The association of persistent rhinitis and asthma is a well-defined clinical entity within the ''one airway, one disease'' concept. However, accompaniment of analgesic intolerance (AI), seasonal rhinitis (SR) or chronic urticaria (CU) to asthma are encountered at a relatively lower frequency. Therefore, in this study, we aimed to compare the patients with asthma diagnosis alone with the patients, who, in addition to their asthma, had accompanying AI, CU or SR and to evaluate if there are any clinical or demographical distinctions and specific characteristics of these defined groups.

Patients and methods

In our study, the patient group with asthma diagnosis alone was taken as reference group and comparison of the asthmatic patients with associated AI, CU, or SR was planned. Archieves of the Adult Allergy Unit of Chest Diseases Department were consulted for the selection of the patients from the defined patient groups.

From the archive encompassing the period between 1991 and 2007, primarily asthmatic patients with SR and CU who were thought to be fewer, were investigated. Records of 84 and 46 patients respectively were determined and included in the study. Subsequently, the archive was screened from 2007 backwards, and the files of 84 asthma patients with AI and 84 patients with asthma diagnosis alone were determined in accordance with the number of asthma patients with SR. From these files, 75 asthma patients with AI and as a control group 71 patients with asthma diagnosis alone, who had complete data, were enrolled in the study.

The diagnosis of asthma was in accordance with Global Initiative for Asthma (GINA) guidelines. Patients describing nasal symptoms such as sneezing, rhinorea, nasal itching and congestion seasonally, were considered as SR patients. Patients with recurrent, self-limiting, itchy plaques or angio-oedema persisting for more than six weeks were defined as CU. Diagnosis of AI was made based on placebo controlled oral provocation tests or at least two reliable histories of analgesic intolerance.

From the files demographic data, age at onset for asthma and additional diseases was determined. Moreover, information about familial atopy, keeping pets, and Ear Nose Throat (ENT) surgery was compiled. Pulmonary function tests (PFT) at the time of diagnosis were compiled and body mass indexes (BMI) were calculated based on parameters of heights and body weights derived from these measurements.

Skin prick tests (SPTs) were collected under four main categories: house dust mites, pollens, fungi and animal epithels. Wheals with a mean diameter at least 3 mm more than that of the control are considered as positive cases. Since different proportions of patients without SPTs were encountered among defined patient groups, prick test results were given both including and excluding patients without prick tests. Patients who had any positive prick test were accepted as atopic asthma patient.

Severity of asthma was divided into three categories in accordance with GINA classification as mild, moderate, and severe in consideration of pulmonary function tests and clinical features. Since patients in the severe category were scarce in number, cases in the severe and moderate categories were combined and analysed.

Statistical Analyses: Data of the patient groups included in the study were expressed as mean $\pm$ SD for continuous, and as the number of cases and percentages for categorical variables. For comparisons between patient groups, one-way ANOVA test for continuous, and *Chi*-square test for categoric variables were used. Fisher's exact test was used when 25% of or more of the expected cell count was less than 5. Bonferroni correction was applied for multiple comparisons. In pairwise comparisons, the group of patients with asthma diagnosis alone was used as control group. In comparisons for the severity of asthma, moderate and severe categories were combined due to scarcity of severe asthma patients. Multiple logistic regression models were established to investigate the independent association between asthma phenotypes and the severity of asthma. In these models, combination of moderate and severe asthma was taken as dependent variable, and independent association between asthma phenotypes and the severity of asthma was presented as odds ratio (OR) and 95% confidence interval (CI) calculated using Wald method. Confounding factors included in the models were: age, gender, and factors associated with the severity of asthma in the univariate analysis. Statistical significance was defined for p values less than 0.05. Statistical Package for Social Sciences (SPSS) 10.0 for Windows was used in the statistical analysis.

Results

Eighty-four asthma patients diagnosed with asthma and SR, 46 with asthma and CU, 75 with asthma and AI, and 71 patients with asthma alone were enrolled to the study. The patient characteristics according to disease groups are shown in Table 1. The mean age of all patients was 37.2 ± 13 (15–80) years and 195 (70.7%) were females. The mean age of asthmatic patients with SR at the time of diagnosis was significantly lower than that of the control group (31.9 ± 10.4 and 40.9 ± 14.9 years, respectively; $p < 0.001$). A total of 79 patients (28.6%) were current smokers. Distribution of genders and smoking status did not differ among patient groups. Compared to the reference

Table 1 Demographic characteristics of asthma groups

	Asthma and AI (n=75)	Asthma and CU (n=46)	Asthma and SR (n=84)	Asthma (n=71)	Total (n=276)	P*
Age, years[a]	39.9±12.5	36.9±11.6	31.9±10.4***	40.9±14.9	37.2±13	**<0.001**
Female, n (%)	57 (76)	36 (78.3)	55 (65.5)	47 (66.2)	195 (70.7)	0.253
Family atopy, n (%)	47 (62.7)	30 (66.7)	57(67.9)	38 (53.5)	172 (62.3)	0.283
Pet keeping, n (%)	11 (14.7)	3 (6.5)	7 (8.3)	10 (14.1)	31 (11.2)	0.362
ENT operation, (%)[b]	22 (29.3)***	6 (13)	5 (6)	8 (11.3)	41 (14.9)	**<0.001**
Age of asthma onset, years[a]	30.1±11.6	31.3±12.5	27.4±10.8**	34.5±16	30.6±13	**<0.01**
Age of AI onset, years	32.9±13					
Age of CU onset, years		30.8±15.2				
Age of SR onset, years			24.3±4.3			

In pairwise comparisons, patients with only asthma diagnosis were used as control group.
In pairwise comparisons, after the Bonferroni correction: *p<0.05; **p<0.001; ***p<0.01.
[a]Statistical significance in comparison between asthma with SR and control asthma group.
[b]Statistical significance in comparison between asthma with AI and control asthma group.

Table 2 Distribution of skin prick test results according to asthma groups

	Asthma and AI (n=75)	Asthma and CU (n=46)	Asthma and SR (n=84)	Asthma (n=71)	p*
Prick (+) %	24	37	92.9	26.8	
Prick (−) %	56	30.4	7.1	66.2	
Not done %	20	32.6	0	7	
After excluding the patients without prick tests					
Prick (+)[a] **%**	30	54.8	92.9***	28.8	**<0.001**
Prick (−) %	70	45.2	7.1	71.2	
Distribution according to allergen groups					
Pollens (+)[a]	5 (8.2%)	7 (22.6%)	76 (90.5%)***	7 (10.6%)	**<0.001**
Mites (+)	13 (21.3%)	10 (32.3%)	15 (17.9%)	12 (18.2%)	0.36
Animal epith. (+)	4 (6.6%)	1 (3.2%)	8 (9.5%)	2 (3%)	0.359
Fungi (+)	4 (6.6%)	2 (6.5%)	3 (3.6%)	1 (1.5%)	0.469

In pairwise comparisons, patients with only asthma diagnosis were used as control group.
In pairwise comparisons, after the Bonferroni correction: *p<0.05; **p<0.001; ***p<0.01.
[a]Statistical significance in comparison between asthma with SR and control asthma group.

group, asthma patients with SR had a significantly earlier onset of asthma (age: 34.5±15.9, and 27.4±10.8; respectively, $p<0.01$). Prevalence of any familial atopic disease, and keeping a pet at home were found as 62.5 and 11.2%, respectively, without a significant difference between groups. Asthma patients with analgesic intolerance had a significantly higher rate of nasal operations (29.3% and 11.3%; respectively, $p<0.05$).

The distribution of SPT results according to patient groups is shown in Table 2. In analysis performed after excluding the patients for whom prick test had not been performed, in the group of asthma patients with SR, significantly higher rates of atopy were detected compared to the reference group (92.9% and 28.8%, respectively; $p<0.001$). When the distribution of allergens according to asthma groups was analysed, sensitivity to pollens was significantly more frequently detected in the asthma patients with SR (90.5% and 10.6%, respectively; $p<0.001$). The distribution of other allergens did not differ among defined asthma groups.

When PFTs of disease groups were compared, in the asthma patients with SR, mean FVC (91.5±12.4% and 83.6±18.7%, respectively; $p<0.01$), FEV1 (89.1±14.2% and 77.7±19.4%, respectively; $p<0.001$), and $FEF_{\%25-75}$ (76.9±22.5% and 63.5±24.4%; $p<0.01$) were higher than the reference group. The lowest PFT values, although the differences were not significant, were detected in the asthma patients with AI (Table 3).

Table 4 demonstrates the distribution of the severity of asthma in asthma groups. In asthma patients with SR, the incidence of mild asthma was significantly higher (83.3% and 56.3%, respectively; $p<0.001$). Although moderate-to-severe degrees of asthma were encountered most frequently in asthma patients with AI, differences were not significant (52% and 43.7%, respectively; $p>0.05$).

Table 3 Pulmonary function tests of asthma groups

	Asthma and AI (n=75)	Asthma and CU (n=46)	Asthma and SR (n=84)	Asthma (n=71)	p*
FVC[a]	2.96±1.1	3.29±0.89	3.68±1.06*	3.15±1.18	**<0.001**
FVC%[a]	83±21	90.5±19.7	91.5±12.4**	83.6±18.7	**0.004**
FEV1	2.32±1	2.67±0.75	3.02±0.84	2.48±0.92	0.458
FEV1%[a]	76.4±25	86.4±21	89.1±14.2***	77.7±19.4	**<0.001**
FEV1/FVC %	77.7±13.6	83.8±13.2	83.5±8.5	79.7±11.7	**0.004**
$FEF_{\%2575}$[a]	64±30.1	73.2±25.1	76.9±22.5***	63.5±24.4	**0.002**

In pairwise comparisons, patients with only asthma diagnosis were used as control group.
In pairwise comparisons, after the Bonferroni correction: *p<0.05; **p<0.001; ***p<0.01.
[a]Statistical significance in comparison between asthma with SR and control asthma group.

Table 4 Distribution of the severity of asthma in asthma groups

Severity	Asthma and AI (n=75)	Asthma and CU (n=46)	Asthma and SR (n=84)	Asthma (n=71)
Mild	36 (48%)	31 (67.4%)	**70 (83.3%)**	40 (56.3%)
Moderate	20 (26.7%)	10 (21.7%)	**13 (15.5%)***	22 (31%)
Severe	19 (25.3%)	5 (10. 9%)	**1 (1.2%)****	9 (12.7%)
P (vs. only asthma)[a]	0.15	0.09	**0.0003**	reference
After the combination of moderate and severe categories				
Mild[b]	36 (48%)	31 (67.4%)	**70 (83.3%)**	40 (56.3%)
Mod-severe	39 (52%)	15 (32.6%)	**14 (16.7%)**	31 (43.7%)
P (vs. only Asthma)	0.31	0.23	**0.0002**	reference

In pairwise comparisons with mild asthma, after the Bonferroni corrections: *p<0.01, p<0.001.
[a]In pairwise comparisons, patients with only asthma diagnosis were used as control.

Table 5 Associations between the severity of asthma and the patient characteristics

	Mild (n=177)	Moderate-Severe (n=99)	p
Skin prick test* (+)	95 (61.3%)	37 (43.0%)	**0.006**
Pollen* (+)	74 (47.7%)	21 (24.1%)	**<0.001**
Mites* (+)	30 (19.4%)	20 (23.0%)	0.503
Animal epithel* (+)	10 (6.5%)	5 (5.7%)	0.827
Fungi* (+)	4 (4.5%)	3 (3.4%)	1.0
Gender			
Female	125 (70.6%)	70 (70.7%)	0.988
Male	52 (29. 4%)	29 (29.3%)	
Smoking (+)	49 (27.7%)	30 (30.3%)	0.644
Family atopy	112 (63.6%)	60 (60.6%)	0.618
Pet keeping (+)	17 (9.6%)	14 (14.1%)	0.252
ENT operation (+)	24 (13.6%)	17 (17. 2%)	0.418
Age	34.8±11.4	41.6±14.4	**<0.001**
Smoking (pack/year)	9.0±8.3	13.9±12.0	0.069
Median (range)	6.2 (1 −3 8)	10.0 (1 −4 5)	
Age of asthma onset	29.4±12.2	32.8±14.1	**0.035**
Age of CU onset	28.8±14.8	34.5±15.2	0.213
Age of AI onset	29.3±11.2	35.7±13.5	**0.02**
Age of SR onset	25.3±10.8	18.8±7.2	**0.04**
Age of polyp onset	26.5±5.8	29.1±14.1	0.622
BMI	24.9±4.4	26.2±5.2	**0.036**

*After excluding the patients without prick tests.

Table 6 Logistic regression models for association between the severity of asthma and asthma groups

	Asthma	AI	CU	SR
Moderate-Severe asthma n (%)	31 (43.7)	39 (52.0)	15 (32.6)	14 (16.7)
Crude OR	1	1.4 (0.8–1.6)	0.6 (0.3–1.3)	**0.6 (0.5–0.8)**
Model OR				
age, gender	1	1.5 (0.8–2.9)	0.7 (0.3–1.6)	**0.3 (0.2–0.7)**
+ age of asthma onset	1	1.4 (0.7–2.7)	0.7 (0.3–1.6)	**0.3 (0.2–0.7)**
+ atopy	1	1.8 (0.9–3.7)	0.7 (0.3–1.8)	**0.3 (0.1–0.7)**
+ pollen sensitivity	1	1.9 (0.9–3.8)	0.7 (0.3–1.8)	**0.3 (0.1–0.8)**
+ atopy+pollen sensitivity	1	1.8 (0.9–3.7)	0.7 (0.3–1.8)	**0.3 (0.1–0.8)**
+ BMI	1	1.5 (0.8–3.0)	0.7 (0.3–1.6)	**0.3 (0.2–0.7)**
+ all	1	1.6 (0.8–3.5)	0.7 (0.3–1.8)	**0.3 (0.1–0.8)**

In Table 5, the association between the severity of asthma and the patient characteristics was demonstrated. When moderate-severe asthma patients were compared with mild asthma patients, prick test positivity (43.0% and 61.3%, respectively; $p<0.01$), and pollen sensitivity (24.1% and 47.7%, respectively; $p<0.001$) were significantly lower. Patients' ages (41.6 ± 14.4 years and 34.8 ± 11.4 years, respectively; $p<0.001$) and BMIs ($26.2\pm5.2\%$ and $24.9\pm4.4\%$; $p<0.01$) were higher in moderate-to- severe degrees of asthma.

Independent association between the severity of asthma and asthma phenotypes was investigated in logistic regression models. Asthma phenotypes and confounding factors were included in models in which moderate-to-severe asthma was the dependent variable and the group with asthma alone was the reference group. The confounding factors included were age, gender, the onset of asthma, atopy, sensitivity to pollens, and BMI, which were related to the severity of asthma and asthma phenotypes. According to the results of the model shown in Table 6, a significant negative association between moderate-to-severe asthma and SR was detected (OR:0.6 95% CI: 0.5–0.8).

Discussion

In this study, the association of the defined asthma phenotypes with patient characteristics and the severity of asthma were assessed. According to these assessments, in patients with SR, significantly earlier onset of asthma, better pulmonary functions and higher rates of atopy were observed. The severity of asthma was milder in atopic patients and among them those with pollen hypersensitivity; and also, asthma became more severe with increasing in patient's age, age at onset of asthma, and BMI. In logistic regression models, a negative association between moderate-to-severe asthma and SR was detected. (OR:0.6 95% CI: 0.5–0.8) Asthma associated with AI, although not statistically significant, was more severe than the reference asthma group.

Increased sensitivity to non-specific bronchial provocation tests has been recognised in the pollen season in patients with seasonal allergic rhinitis[6] and even asymptomatic bronchial hyperactivity has been thought to be associated with the development of asthma.[5] Within this context, the concomitant presence of SR and asthma is not very surprising. In this study, we found that the mean age of asthma patients with SR at the time of diagnosis (31.9 yrs) and also at the onset of their asthma (27.4 yrs) were found to be significantly lower compared to the reference group. In Western countries SR onsets relatively at an earlier age (15 yrs),[7] while it was found to be 24.3 years in this study. This finding can be related to the differences in herbal flora in our country, ignorance of certain diseases and a cultural tendency to look for medical help too late. On the other hand, rhinitis is known to be an independent risk factor for the development of asthma.[8] Therefore, earlier onset of asthma associated with SR, compared with the patients with asthma diagnosis alone, whose development is probably under the influence of different environmental factors, can be accepted as a natural phenomenon. In a study where clinical features of asthma patients with SR, and persistent asthma patients were compared, it was observed that in asthma patients with SR, the values of FEV1 and FEF 25–75 were higher, and these patients were more symptomatic despite better respiratory functions.[9] Although symptoms of patients in defined groups were not assessed, FVC, FEV1, FEV1/FVC, FEF25–75 percentages were also found to be significantly higher in asthma patients with SR compared to the reference group in our study. Although not significantly different from the reference group, the lowest values for PFTs were observed in asthma patients with AI, while asthma patients with CU had the best PFTs ranking after those with SR.

Controversial results have been obtained from studies investigating the association between asthma and atopy. In developed countries, the prevalence of atopy, and asthma increases concomitantly,[10] while in developing countries the increases in the prevalences of asthma and atopy do not parallel each other.[11] These findings indicate that in some patients the development of asthma is not correlated with atopy. In a meta-analysis of various epidemiological studies, it was concluded that in only less than fifty percent of the patients, the development of asthma could be attributed to the presence of atopy.[12] On the other hand, clinical manifestations caused by different allergens can be different. Indoor inhalant allergens such as mites and cat epithels were found to be more closely associated with asthma, while pollens which are retained within the nasal mucosa, and induce local allergic reactions because of their bigger

sizes have been usually found to be related to rhinitis.[13] In this study, sensitivity to inhalant allergens was significantly more pronounced in comparison with the reference group in asthma patients with SR (92.9% and 28.8%, respectively). When the distribution of allergen groups according to defined groups was examined, the prevalance of pollen sensitivity was significantly higher in asthma patients with SR relative to the reference group (90.5% and 10.6, respectively). There was no difference in the distribution of other allergens among defined asthma groups. When a high rate of pollen sensitivity in asthmatic patients with SR was discarded, the most frequent inhalant allergen was mite, which was in accordance with previous studies.

Asthma is a disease of variable severity. Severe and uncontrolled asthma patients go to emergency room more often, they are more frequently hospitalised and carry a risk of death. Therefore, the detection of risk factors which determine asthma severity is important for the treatment and the prediction of the disease prognosis. Another issue which should be known is that aetiological factors of a disease, and those determining its severity are not always identical. Asthma is one of the examplary diseases. Although there are many epidemiological data which indicate an association between atopy and prevalence and symptoms of asthma,[13,14] the association between atopy and the severity of asthma is more ambiguous. In our study when the association between the patients' characteristics and the severity of asthma was evaluated, those with prick test positivity had significantly milder asthma. When allergen groups and the severity of asthma were investigated, pollen-sensitive patients were significantly associated with mild asthma. Sensitivity to mites, animal epithel and fungi were also more frequently seen in mild asthma compared to moderate-to-severe asthma although the difference was not significant. On this subject controversial information is available in the literature. Analysis of TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) cohort which consists of severe or difficult-to-treat asthma patients such as the ones prick test positive, negative and those without prick test has showed that 93.5% of the tested patients had positive prick tests. Although these results might seem to suggest an association between severe asthma and skin test positivity at first sight, severity of asthma evaluated by FEV1 values, oral steroid usage, hospitalisation rates, health costs and QoL scores did not differ significantly among the three groups.[15] In a study where the patients from ENFUMOSA (The European Network For Understanding Mechanisms Of Severe Asthma) cohort were evaluated, a negative association was detected between patients' self-reported personal and familial history of allergy and severe asthma.[16] In a study where paediatric patients recruited from the EGEA (Epidemiological study on the Genetics and Environment of Asthma) study were investigated as for the relationship between allergic sensitivity, total IgE, blood eosinophil counts and the severity of asthma, no association was found between the severity of asthma and sensitivity to any inhalant allergen or allergen subgroups such as indoor or outdoor allergens, and moulds.[17] Similar findings were observed in adult studies.[18,19] According to these outcomes, inhalent allergen sensitivity known to be associated with the prevalence of asthma seems to have no influence on the severity of asthma. These results also support the hypothesis that the development and the severity of asthma might be under the influence of different environmental and genetic risk factors.

Chronic urticaria is a skin disease, where migratory and transient itchy plaques are frequently associated with angio-oedema, and it persists longer than six weeks. The main mediator in its pathogenesis is vasopermeability inducing histamine and which is released from mast cells and basophils. Moreover, the synthesis of cystenil leukotrienes in basophils was increased in the sera of some patients with CU, especially in patients with autologous serum test positivity.[20] On the other hand, histamine and leukotrienes are also known to stimulate smooth muscles of the respiratory tract leading to bronchospasm.[21] There are also some other reasons that the coexistence of two diseases can be accepted as a conjunct outcome of multiple patogenetic components rather than a coincidence.[22–24] Despite this fact, studies investigating the coexistence of CU and asthma are very few in number. In a study where 26 patients with CU and 26 asthma patients as controls were enrolled, 22 patients with CU (85%) demonstrated bronchial hyperactivity and two of these patients (8%) were diagnosed with asthma before the test. When compared with asthma patients, bronchial hyperactivity in CU patients was found to be milder.[25] Bronchial hyperresponsiveness in CU patients was explained by the results of two studies showing that the immunopathology of CU was that of an eosinophil and basophil cell-mediated hypersensitivity reaction with a TH0, or a mixture of both TH1 and TH2 cytokine profile.[26,27] Also, in a study that consists of only 12 patients, none of the cases showed bronchial hyperactivity.[28] In a study conducted in our clinic, the prevalence of asthma was found to be 16.4% in CU patients with AI, while this rate was 8.4% in patients without AI.[29] In this study when asthma patients with CU were compared with the reference asthma group, no difference was detected in any of the demographic data and parameters which potentially might have an impact on the severity of asthma. However, they had a tendency to demonstrate better pulmonary functions, milder asthma severity, and higher rates of hypersensitivity to inhalant alergens when compared with asthmatic patients with AI and the reference group.

In many parts of the world, especially during the last 20–30 years, obesity has become an important health problem, and its prevalence is increasing, particularly in developed countries.[30] The observation of a similar increase in the prevalence of asthma has led to investigations searching the association between these two disease states. Many epidemiological studies and meta-analyses have clearly revealed the association between obesity and asthma, although existence of any causality in this association is still controversial.[31,32] In recent years the effects of obesity on the management and severity of asthma have been increasingly investigated. Using the data of the National Asthma Survey, which was one of the most comprehensive asthma studies performed in the United States, obesity was found to be correlated with asthma symptoms, school absenteism, drug usage, and GINA's classification of severity of asthma.[33] In another study, after corrections were performed for potential confounding factors such as age; smoking status; FEV1; and bronchial

hyperactivity, obesity was considered as a risk factor for the severity of asthma only in women.[34] On the other hand, in a longitudinal study performed in Europe, no difference was found among baseline BMIs of the patients regarding asthma severity. However, during follow-up, asthma patients who remitted were observed to gain less weight.[35] In this study, when the severity of asthma was divided into the two categories of mild and moderate-to-severe, the BMIs of the moderate-to-severe asthma patients significantly exceed those of the mild asthma patients (24.9 ± 4.4 and 26.2 ± 5.2, respectively). It is known that BMI values between 25.00–29.99, and ≥ 30 are classified as overweight and obesity, respectively. Interestingly, our findings demonstrated that BMIs around but slightly higher than normal limits (i.e. 26.2) were associated with moderate-to-severe asthma, and the BMI values of the two severity groups could probably be found over and below the accepted upper limit of normal (i.e 25) healthy subjects (mild asthma: 20.5–29.3; moderate-to-severe asthma 21.0–31.4). Our findings, and previous data in the literature, give the impression that obesity is associated with more severe asthma, worse asthma control and lower quality of life scores, and suggest that weight control should be an important target in the monitorisation of asthma patients.

There are strong associations between asthma, persistent rhinitis/sinusitis, nasal polyp(s) and AI. The prevalence of nasal polyps in the population is 0.6%, 6–15% in asthma patients and as high as 70% in analgesic intolerant asthma (AIA),[36,37] while rhinosinusitis is seen radiologically in nearly all AIA patients.[38] Since the response of AIA phenotype to corticosteroids is generally poor, the asthma of these patients is severe. In a study which used the cohort of the TENOR study, it was seen that AIA patients had lower post-bronchodilator FEV1 values and more severe clinical asthma, used higher doses of oral and inhaled corticosteroids, and were intubated more frequently.[39] Also in our study, nasal pathologies of the patients were evaluated in consideration of their ENT operation history, and medical histories of patients with AI revealed a significantly higher number of ENT operations (29.3% vs. 11.3%). Because odds ratios of the patients with AI varied between 1.4 and 1.9, and the lower limits of 95% confidence interval were very close to 1 in various models where severity of defined asthma groups compared to reference group, although lacking statistical significance, asthma patients with AI were thought to have more severe forms of the disease as in accordance with the literature findings. It seems that nasal symptoms and physical finding of rhinosinusitis and/or polyp might be inadequate in defining AIA while AI per se is a satisfactory indicator of this disease state.

Since the number of severe asthma cases was too low (as an example, severe asthma with SR was only one patient), moderate and severe asthma categories had to be combined in the logistic regression analysis. This might be the limitation of analyses used for evaluating asthma severity.

As a conclusion, asthma associated with CU, which was thought to be a new phenotype in our hypothesis, has not manifested a distinct phenotypic feature. However, it was observed that asthma associated with SR has a significantly earlier onset with more frequent atopy, and milder severity. Asthma associated with AI tends to be more severe. Information concerning SR is original and provides hints regarding the definition of a new phenotype. Our findings indicate the importance of further investigations in this field.

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