Allergology International. 2009;58:549-555
DOI: 10.2332/allergolint.09-OA-0093

ORIGINAL ARTICLE

The Relationship between Asthma and Allergic Rhinitis in the Iraqi Population

Abdulghani Mohamad Alsamarai[1], Ammar M Alwan[1], Amina Hamed Ahmad[1], Mohib Ahmad Salih[1], Jawad Ali Salih[1], Mohamad Abdulsatar Aldabagh[1], Safa Alturaihi[1], Zainab Hashim Abdulaziz[1], Anas Ahmad Salih[1], Sana Khalaf Salih[1] and Mossa Mahmood Murbat[1]

ABSTRACT

Background: Recently, extensive research has established that epidemiologic and therapeutic links exist between allergic rhinitis and asthma. The objective of this study was to clarify this association in Iraq.

Methods: The data included in this study were collected from five surveys for asthma and allergic rhinitis that were performed during the period from September 2000 to July 2008. These surveys were parts of Tikrit University College of Medicine PHC program.

Results: The frequency of allergic rhinitis (AR) was 61.6% among individuals with asthma versus 6% among non-asthmatic (control) subjects (Odd Ratio [OR] = 25.5; $P < 0.0001$). All studies indicated a significant frequency of AR among asthmatic patients in comparison with non-asthmatic subjects, whether the patients were adults or children (OR for adults = 14.9 and 22.5, for children 34.7 and 48.4; $P < 0.001$ for all). Furthermore, the high frequency of AR in asthmatic patients was seen whether the study was a community based study (CBS) (OR = 14.9 and 48.4; $P < 0.0001$) or a hospital based study (HBS) (OR = 22.5 & 34.7; $P < 0.0001$). The frequency of current asthma was 51.8% among individuals with AR versus 5.4% among control subjects (OR = 23.1; $P < 0.0001$).

Conclusions: This study provided evidence that AR and asthma are strongly associated with each other and the treatment approach should consider the entire airway rather than only a part.

KEY WORDS

allergen, allergic rhinitis, allergy, asthma

INTRODUCTION

Asthma is one of the most common chronic diseases worldwide.[1] A large percentage of children and adults with asthma also have allergic rhinitis (AR).[2] The link between AR and asthma has long been of interest to physicians. Recently, extensive research has established that epidemiologic and therapeutic links exist between AR and asthma.[3] A number of epidemiologic studies have shown an association between asthma and allergic rhinitis. In a review of five large studies that included populations of children and adults,[4] the prevalence of asthma ranged from 3.6% to 5% in subject without rhinitis versus 10.8% to 32% in subject with rhinitis. In a 23 year follow-up study in university students,[5] asthma developed in 10.5% of subjects with AR, whereas it developed in only 3.6% of subjects without AR. In addition, the reported lifetime prevalence of AR among adults with asthma ranges from 50% to 100%, varying by study design and geographical areas.[6]

Asthma and AR are both inflammatory diseases of the airways. The similarities between AR and asthma in epidemiologic and pathophysiologic features suggest that AR and asthma represent the same syndrome, the chronic allergic respiratory syndrome.[7] A report of the American Academy of Allergy, Asthma, and Immunology[8] estimated that up to 78% of patients with asthma have nasal symptoms and 38% of patients with AR have asthma. While there are several surveys assessing the association between AR and asthma in different geographical areas worldwide, none were performed in large scale studies. Thus, this study was performed to clarify this association in Iraq.

[1]Department of Medicine, College of Medicine, Tikrit University, Salahuldean, Iraq.
Correspondence: Abdulghani M. Alsamarai, Department of Medicine, College of Medicine, Tikrit University, P O Box 45, Alyarmook ST, Tikrit, Salahuldean,, Iraq.
Email: galsamarrai@yahoo.com
Received 30 January 2009. Accepted for publication 1 May 2009.

Table 1 Study population

Study	Residence	Age	Type	Number examined
1	Rural	Adult	Community based study	1384
2	Urban	Adult	Hospital based study	8687
		Children	Hospital based study	3780
3	Urban	Children	Community based study	2875
4	Urban & rural	Mixed	Hospital based study	9317
5	Urban & rural	Mixed	Hospital based study	8747

METHODS

STUDY POPULATION

The data included in this study was collected from five surveys for asthma and allergic rhinitis that were performed during the period from September 2000 to July 2008. These surveys were part of Tikrit University College of Medicine PHC program. (Table 1).

The first survey was a community-based study that was performed in Al-Hjaj village (rural area) to determine the prevalence of bronchial asthma in adults. 1384 individuals were included in this cross-sectional study. This number represents all adults of the village. The village was located 40 miles from Tikrit city. This study was carried out during the period from September 18, 2002 to December 3, 2002. The age range of the study population was from 18 to 45 years and 760 (54.9%) were men and 624 (45.1%) were women.

The second survey was a hospital-based study that included a mixed population from urban and rural areas. This included the patients attending the Tikrit Allergy and Asthma Centre during the period from September 2000 to July 2008. 12467 patients were included in the study, of them 8687 (69.7%) were adults, and 3780 (30.3%) were children.

The third survey was a community-based study that included primary school children in Samara city (urban area). The children were all preadolescent school age children. The total number of primary school children in Samara city was 10820 children, 5397 boys and 5423 girls. We chose 2875 children in grade 5 and 6, 1624 (56.5%) boys and 1251 (43.5%) girls. These two grades were selected because these grades performed the exercise challenge and peak flow metric measures better than younger age groups and the questionnaire data obtained from them were more accurate.

The fourth survey was a hospital-based study performed at Tikrit Teaching Hospital to determine the epidemiological characteristic of allergic rhinitis. The study population was a mixture of rural and urban inhabitants. A total number of 9317 individuals were included in the study, of them 5198 (55.8 %) were men and 4119 (44.2 %) were women.

The fifth survey was a hospital-based study performed in Samara General Hospital during the period from September 2000 to July 2008 to determine the epidemiological characteristics of AR in Samara. The population was a mixture of rural and urban individuals both men and women. A total of 8748 patients were included in the analysis, of them 5608 (64.1 %) were men and 3140 (35.9 %) were women.

Eosinophil cationic protein (ECP, as a marker of eosinophil), malondialdehyde (MDA) and total antioxidant capacity (TAC) (as markers of oxidative stress) were determined in 100 patients with AR alone/100 patients with asthma alone/100 patients with AR and asthma together and in 50 healthy controls.

ASTHMA AND ALLERGIC RHINITIS DIAGNOSIS

The diagnosis of asthma and classification was performed by specialist physicians based on the National Heart Blood and Lung Institute/World Health Organization (NHLBI/WHO) workshop on the Global Strategy for Asthma.[9] Allergic rhinitis diagnosis was performed according to previously reported guidelines.[10] Patients were excluded if they were smokers, if they had respiratory infection within the month preceding the study, a rheumatological illness, malignancy, diabetes, heart failure, history of venous embolisms, coronary heart disease and liver or kidney diseases. At enrollment, they all underwent a full clinical examination, pulmonary function test, and blood sampling.

DETERMINATION OF TOTAL ANTIOXIDANT CAPACITY

The method for serum TAC determination as previously described by Kampa M *et al.*[11] was used.

DETERMINATION OF MALONDIALDEHYDE

Serum MDA concentration was determined by measuring the thiobarbituric acid reactive substances (TBARS) according to the spectrophotometric method of Janero.[12] The TBARS was determined using OXITEK TBARS Assay kit from Zeptometrix Corporation (Buffalo, NY, USA).

DETERMINATION OF OXIDATION INDEX

The index was determined by the following equation.

Table 2 Frequency distribution of allergic rhinitis in asthmatic patients and non-asthmatic patients

Study	Age	Frequency of allergic rhinitis						OR
		Asthmatic patients			Non-asthmatic patients			
		No.	AR	%	No.	AR	%	
1	Adult	104	65	62.9	1280	129	10.1	14.9
2	Adult	1036	490	47.3	7661	294	3.8	22.5
	Children	308	91	29.5	3472	42	1.2	34.7
3	Children	256	192	74.9	2619	153	5.8	48.4
Total	Adult	1140	555	70.3	8941	423	7.2	16.9
	Children	564	283	56.9	6091	195	5.1	30.5
	All	1604	838	61.6	15032	618	6.0	25.5

$$\frac{\text{Mean value of MDA}}{\text{Mean value of TAC}} \times 1000$$

DETERMINATION OF SERUM EOSINOPHILS CATIONIC PROTEIN

Serum ECP was determined by ELISA kit (MBL MESCACUP ECP TEST) from Medical and Biological Laboratories Co, LTD, Nagoya, Japan.

STATISTICAL ANALYSIS

Data concerning the comparisons among the various parameters in the study groups are given as mean (SD) with 95% confidence intervals for the differences. Student's unpaired one tailed test was used for significant testing.

RESULTS

Information for 1704 (1140 adults and 564 children) subjects with asthma and 15032 non-asthmatic (control) subjects were analyzed concerning the presence of allergic rhinitis in asthmatic patients (Table 2). The frequency of allergic rhinitis (AR) was 61.6% among individuals with asthma versus 6% among non-asthmatic (control) subjects (OR = 25.5; $P < 0.0001$). When the analysis was performed after classification of asthmatic patients into adults and children there was still a positive association between frequency of AR and asthma ($P < 0.0001$). For adults the frequency of AR was 70.3% among adults with asthma versus 7.2% among non-asthmatic adults, (OR = 16.9; $P < 0.0001$), while in children the frequency of AR among asthmatic patients was 56.9% versus 5.1% among non-asthmatic children (OR = 30.5; $P < 0.0001$) as shown in Table 2. All studies indicated a significant frequency of AR among asthmatic patients in comparison with non-asthmatic subjects, whether the patients were adults or children (OR for adults = 14.9 and 22.5, for children 34.7 and 48.4; $P < 0.001$ for all). Furthermore, the high frequency of AR in asthmatic patients was seen whether the study was CBS (OR = 14.9 and 48.4; $P < 0.0001$) or HBS (OR = 22.5 and 34.7; $P < 0.0001$).

The information for 1682 subjects with AR and 28849 non-allergic rhinitis individuals (control) was analyzed concerning the presence of asthma in patients with AR (Table 3). The frequency of current asthma was 51.8% among individuals with AR versus 5.4% among control subjects (OR = 23.1; $P < 0.0001$). When data of AR was evaluated for each survey alone, frequencies were of 32.8%, 42.5%, and 63.4% for asthma among individuals with AR in surveys 4, 5 and 2 respectively. These frequencies were significantly higher (OR = 11, 13.8, and 24.4; $P < 0.0001$) than those of individuals without AR (Table 3). Furthermore, the differences in frequency of asthma among AR individuals were significantly higher ($P < 0.0001$), whether the patients were adults (62.5%; OR = 22.5) or children (68.4%; OR = 34.2).

Comparison of mean serum level of ECP, MDA, and TAC in patients with AR alone, asthma alone and presence of both conditions in the same group indicated differences in their values between groups (Table 4). The mean serum level of ECP was significantly higher in the three groups as compared to control ($P < 0.0001$). However, there were significant differences ($P < 0.0001$) in the mean serum ECP values between the AR alone group (14.85 ± 8.23 µg/l, Confidence Interval 13.25-16.45 µg/l), the asthma alone group (36.12 ± 12.76 µg/l, Confidence Interval 32.6-39.6 µg/l) and the group of patients with both AR and asthma together (58.21 ± 13.6 µg/l, Confidence Interval 55.5-60.9). Concerning MDA there was a significant increase in serum level mean values between the three groups and the control ($P < 0.0001$). In addition, patients with both AR and asthma (7.23 ± 2.82 µmol/l, Confidence Interval 6.6-7.8) had a mean value of serum MDA significantly ($P < 0.0001$) higher than that in patients with AR alone (3.49 ± 1.84 µmol/l, Confidence Interval 3.1-3.9) or patients with asthma alone (4.41 ± 1.9 µmol/l, Confidence Interval 4.04-4.78). However, the difference between mean serum MDA values in patients with asthma alone (4.41 µmol/l) and patients with AR alone (3.49 µmol/l) was not significant. TAC shows a lower level of mean value in patients with AR and asthma (771 ± 162 µmol/l, CI 739-803) as compared to patients with asthma alone

Table 3 Frequency distribution of asthma in patients with and without allergic rhinitis

Study	Age	Asthma						OR
		Allergic rhinitis patients			Non-AR patients			
		No.	Asthma	%	No.	Asthma	%	
4	Mixed	363	119	32.8	8954	381	4.2	11
5	Mixed	402	171	42.5	8345	426	5.1	13.8
2	Mixed	917	581	63.4	11550	763	6.6	24.4
Total		1682	871	51.8	28849	1570	5.4	23.1

Table 4 Serum eosinophilic cationic protein, MDA, TAC and oxidation index in patients with AR and asthma

Group	ECPμg/l	MDA μmol/l	TAC μmol/l	Oxidation Index
Patients with asthma alone	36.12 ± 12.76 (32.64-39.6)	4.41 ± 1.9 (4.04-4.78)	897 ± 178 (862-932)	4.9
Patients with AR alone	14.85 ± 8.23 (13.25-16.45)	3.49 ± 1.84 (3.13-3.85)	986 ± 112 (964-1008)	3.5
Patients with AR and asthma	58.21 ± 13.6 (55.54-60.88)	7.23 ± 2.82 (6.63-7.83)	771 ± 162 (739-803)	9.4
Control	7.68 ± 5.63 (6.08-9.68)	2.24 ± 0.26 (2.16-2.30)	1047 ± 207 (1015-1133)	2.1

(897 ± 178 μmol/l, CI 862-932) and patients with AR alone (987 ± 112 μmol/l, CI 964-1008). However, all three groups had significantly ($P < 0.1$ to 0.001) lower serum values as compared to the control group. The oxidation index was 4 times higher in patients with AR and asthma together than in the control group (2.1), 1.5 times than in patients with AR alone (3.5) and 2 times than in patients with asthma alone (4.9).

DISCUSSION

The results from our analysis of a large cohort consisting of two community-based and hospital-based studies show that there was a relationship between asthma and allergic rhinitis (OR = 11-48.4). The relationship was seen whether the analysis was performed for each survey alone or when the patients were classified into adults and children, or when the five surveys were combined together. The present study showed a prevalence rate of 61.6% of AR in asthmatic patients and there was a significant difference in prevalence rate whether the patients were adults or children or the survey was community-based or hospital-based as compared to subjects without asthma. This result is consistent with the percentage reported for other geographical areas.[6]

Allergic rhinitis is very common in patients with asthma,[13] with a reported prevalence of up to 100% in those with allergic asthma.[14] In a recent review,[6] the point prevalence of AR ranged from 24% to 94% and lifetime prevalence ranged from 50% to 100% among adults with asthma in Europe and in the United States. These findings have been corroborated in more recent studies from Europe and Japan.[15,16] In this study the prevalence rate of AR was 70.3% among adults, 56.9% among children and 61.6% among total patients with asthma. The variability in the reported prevalence of comorbid AR in patients with asthma in the reported studies was attributable in part to differences in diagnostic criteria, study design[6] and perhaps geographical variations due to influence of air pollution.

Geographical differences may exist also.[17] One study from China reported a lower (6%) prevalence of comorbid AR in people with asthma.[18] Among school age children surveyed in the international study of asthma and allergy in children, there are striking variations in the prevalence of asthma and allergic rhinoconjunctivitis symptoms recorded among different centers worldwide[17]; nonetheless, significant correlations are noted between the prevalence of asthma and allergic rhinoconjunctivitis symptoms.[19,20]

Several reported studies have examined the association between AR and asthma. In the Rochester, Minnesota, USA study,[21] the overall prevalence of AR was 52% among their study population. In the UK, Medline-plus general practice databased studies[22,23]; concomitant AR was documented in medical records of only 17% of adult patients and in 20% of children with asthma. Similarly in Norway, AR was documented in 27% of asthmatic children.[24] Recently a study[25] of survey results from four countries each in the Asia-Pacific region and Europe documented that most patients (73%) had pre-existing symptoms of AR when their asthma was first diagnosed.

It is possible that the prevalence of comorbid AR among patients with asthma in these retrospective studies was underestimated because the diagnosis of AR was restricted to that recorded in medical re-

cords,[17] with the exception of that reported by Valovirta,[25] in which the adult patients and parents of children filled a formulated questionnaire which is a potential limitation.

In this study, the team members examined the recruited subjects by surveys (1, 2, and 3) during the study periods and thus the prevalence of comorbid AR may be not underestimated. The possibility that in part may lead to underestimation of AR prevalence in patients with asthma was that many people with AR self manage the condition with over the counter products, and do not seek a physician's help or indeed do not recognize AR as a condition needing treatment.[15] There was a significantly higher frequency of AR in asthmatic children in survey 3 (74.9%) compared to survey 2 (29.5%). This variation may be due to the difference in the study design, since survey 2 was a hospital-based study and while the survey 3 was a community-based study. Concerning epidemiological studies, the community-based studies are more accepted since the individuals in the selected sites are examined.

Asthma is often present in patients with AR.[17] The present study documented a prevalence rate of 51.8% of asthma in patients with allergic rhinitis versus 5.4% in non-AR subjects (OR = 23.1). Linneburg *et al*.[14] reported asthma in 25% of patients with AR who were pollen sensitive and in 50% of those AR patients who were mite-sensitive or animal sensitive. Greisner *et al*[26] reported a history of asthma among 21% of former college students with a cumulative history of AR over 23 years of follow-up. In the European Community Respiratory Health survey, an association between asthma and rhinitis was observed even in nonatopic individuals.[27] This finding implies that the relationship cannot be fully explained by shared risk factors and supports the hypothesis that upper-airway disorders may directly affect the lower airway.[17] However, the reported studies combined indicate that AR is a risk factor for the development of asthma.[5,28-33]

Bronchial hyper-responsiveness is common in people with AR, even if they have no asthma symptoms and asymptomatic airway hyper-responsiveness is associated with increased risk for developing asthma.[34-36] Bronchial inflammation can result from nasal allergen challenge in patients with AR in the absence of obvious asthma.[37] Conversely, patients with asthma can have eosinophilic infiltration of their nasal mucosa without reporting the symptoms of rhinitis.[38,39]

Bronchial asthma and AR are both chronic inflammatory diseases of the upper and lower airway, and the cells mainly responsible for causing this inflammation are eosinophils.[40] Therefore, assessment of serum ECP may be determined to reflect pulmonary inflammation.[41] Studies of asthmatic patients, especially adults, indicated a relationship between the serum ECP level and severity and nature of the disease.[42-45] The present study showed that mean serum ECP levels were higher in subjects with asthma alone, AR alone, or both asthma and AR compared to controls.

This study indicates the role of eosinophilic inflammation in asthma and allergic rhinitis suggesting a significant impact on the management of AR and asthma with anti-inflammatory medication increasingly being recommended as first line therapy. It is clear that our results are consistent with the previous studies that reported a high serum ECP in asthmatic patients[41,46-48] and AR[49,50] when compared with healthy subjects. Serum mean ECP value was significantly higher in patients with the two conditions (AR and asthma) and patients with asthma alone as compared with patients with AR alone, possibly reflecting less activated eosinophils in patients with AR compared to patients with asthma and patients with both conditions.

The present study shows that the three groups of patients had reduced antioxidant capacity as shown by decreased TAC in comparison with the control. In addition, there was a highly significant difference in serum TAC between the three groups. Others[51-53] have reported the reduction in serum TAC in asthmatic and AR patients. The decreased TAC is related to attack and severity[51,53] and the decrease in TAC may result from different mechanisms in patients with asthma and AR as a consequence of increased oxidative stress. Accordingly as a result of the imbalance between oxidative and antioxidant materials, reduction in TAC was achieved. Therefore, it seems that measurement of TAC in serum could be a simple and useful tool in the evaluation of AR and asthma attack and severity. The supplementary administration of antioxidants in the future needs further study and clarification.

The present study indicated that lipid peroxidation as measured by serum MDA level, was increased in patients with AR alone, asthma alone or with both conditions. Furthermore, the increased mean serum levels were significantly different between the three groups of patients. However, the difference in mean serum MDA values between patients with AR alone and asthma alone had marginal significance ($P < 0.05$). Previous reports indicated that plasma and serum MDA levels were higher in patients with asthma[52,54-56] and AR[53] as compared to controls.

The findings from this study suggest that in patients with both asthma and AR, there is local and systemic inflammation, which is more severe when present together. These findings highlight the possibility that comorbid AR may lead to more difficult to control asthma and worsened asthma outcome. The increased serum levels of MDA and decreased TAC observed in the present study indicate increased oxidative stress in AR and asthmatic patients.

In the present study the oxidant/antioxidant bal-

ance seems to be disturbed in asthma and AR as compared to controls. The imbalance between oxidant and antioxidant presented as oxidation index. It was 1.74 times higher in AR, asthma and both disease groups than that in controls. That means the oxidative stress is a prominent event in asthma and AR and its extent is more when the two conditions are present in the same patient. In this respect, the imbalance was higher in patients with both conditions as compared to those with AR alone (3 times) or asthma alone (2 times). This finding suggests that oxidative stress plays an important role in the pathogenesis of AR and asthma and there is a positive correlation between oxidative stress and disease severity. The inflammatory process was the likely source for this imbalance. Both airway and intravascular inflammatory cells contribute to elevated oxidative stress in AR and asthma and this explains why oxidation indexes were high in individuals with comorbid AR in asthmatic patients.

Not all patients with asthma have rhinitis; however, not all patients with rhinitis have asthma. Genetic differences contribute to this discrepancy.[57] Possible mechanisms for the influence of AR on lower airways include disturbance of the beneficial role of nasal mucosa in conditioning the air entering the respiratory tree, neural interaction between upper and lower airways; irritant effects on nasal secretions directly entering the lower airways; and systemic propagation of nasal inflammation to the bronchial mucosa (or vice versa) via effects of mediators and inflammatory cells on bone marrow-systemic cross-talk.[38,39,58]

In conclusion, this study provided evidence that allergic rhinitis and asthma are strongly associated with each other and the treatment approach should consider the entire airway rather than only a part.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;**59**:469-78.
2. Price D, Holgate S. Improving outcomes for asthma patients with allergic rhinitis: the MetaForum conferences. *BMC Pulm Med* 2006;**6** (Suppl 1):S7.
3. Volcheck GW. Does rhinitis lead to asthma? Evidence for the one-airway hypothesis. *Postgrad Med* 2004;**115**:65-8.
4. Leynaert B, Neukirch F, Demoly P, Bouquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000;**106**:S201-5.
5. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;**15**: 21-5.
6. Gaugris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma* 2006;**43**:1-7.
7. Pawankar R. Allergic rhinitis and asthma: are they manifestation of one syndrome? *Clin Exp Allergy* 2006;**36**:1-4.
8. Casale TB, Amin BV. Allergic rhinitis/asthma interrelationships. *Clin Rev Allergy Immunol* 2001;**21**:27-49.
9. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report*. NIH Publication 02-3659. Bethesda, MD: NHLBI, 2002.
10. Dykewicz MS, Fireman S, Skoner DP *et al*. Diagnosis and management of rhinitis: complete guidelines of the joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;**81**: 478-518.
11. Kampa M, Nistikaki A, Tsaousis V, Maliaraki N, Notas G, Gastonas E. A new automated method for the determination of TAC of human plasma based on crocin bleaching assay. *BMC Clin Pathol* 2002;**2**:3-21.
12. Janero D. Malondialdehyde and thiobarbituric acid reactivity as diagnostic indicies of lipid peroxidationand peroxidative tissue injury. *Free Rad Bio Med* 1998;**9**:515-40.
13. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S147-334.
14. Linneberg A, Henrik NN, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002;**57**:1048-52.
15. Nolte H, Nepper Christensen S, Backer V. Unawarness and undertreatment of asthma and allergic rhinitis in a generak population. *Respir Med* 2006;**100**:354-62.
16. Matsuno O, Miyazaki E, Takenaka R *et al*. Links between bronchial asthma and allergic rhinitis in the Oita Prefecture, Japan. *J Asthma* 2006;**43**:165-7.
17. Thomas M. Allergic rhinitis: evidence for impact on asthma. *BMC Pulm Med* 2006;**6** (Suppl 1):S4.
18. Celedon JC, Palmer LJ, Weiss ST, Wang B, Fang Z, Xu X. Asthma, rhinitis, and skin test reactivity to aeroallergens in families of asthmatic subjects in Anqing, China. *Am J Rspir Crit Care Med* 2001;**163**:1108-12.
19. World variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;**351**:1225-32.
20. Strachan D, Sibbald B, Weiland S *et al*. Worldwide vaiations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;**8**:161-76.
21. Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on healthcare charges. *J Allergy Clin Immunol* 1999;**103**:54-9.
22. Thomas M, Kocevar VS, Zhang Q, Yin DD, Price D. Asthma-related health career source use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics* 2005;**115**:129-34.
23. Price D, Zhang Q, Kocevar VS, Yinn DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma related health care use by adults. *Clin Exp Allergy* 2005;**35**:282-7.
24. Sazonov Kocevar V, Thomas J, Jonsson L *et al*. Association between allergic rhinitis and hospital resource use among asthmatic children in Norway. *Allergy* 2005;**60**: 338-42.
25. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. *BMC Pulm Med* 2006;**6** (Suppl 1):S3.
26. Greisner WA, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23 year follow up study of

college students. *Allergy Asthma Proc* 1998;**19**:185-8.
27. Leynaert B, Neukirch C, Kony S *et al*. Association between asthma and rhinitis according to atopic sensitization in a population based study. *J Allergy Clin Immunol* 2004;**113**:86-93.
28. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussing LM. Epidemiology of physicians diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;**94**: 895-901.
29. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finish men and women of the Finish twin cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest* 1999;**115**:928-36.
30. Linna O, Kokkonen J, Lukin M. A 10 year prognosis for childhood allergic rhinitis. *Acta Paediatr* 1992;**81**:100-2.
31. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult onset asthma. *J Allergy Clin Immunol* 2002;**109**:419-25.
32. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med* 2000;**162**:920-4.
33. Leynaert B, Bousquet J, Neukirch C, Lard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;**104**:301-4.
34. Boulet LP. Asymptomatic airway hyperresponsiveness: a curiosity or an opportunity to prevent asthma? *Am J Respir Crit Care Med* 2003;**167**:371-8.
35. Porsbjerg C, Von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12 yeay prospective follow up study. *Chest* 2006;**129**: 309-16.
36. Braman SS, Barrows AA, DeCotiis BA, Settipane GA, Corrao WM. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. *Chest* 1987;**19**:671-4.
37. Bonay M, Neukirch C, Grandsaigne M *et al*. Changes in airway inflammation following nasal allergic challenge in patients with seasonal rhinitis. *Allergy* 2006;**61**:111-8.
38. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;**111**: 1171-83.
39. Gaga M, Lambrou P, Papageorgiou J *et al*. Eosinophils are a feature of upper and lower airway pathology in nonatopic asthma, irrespective of the presence of rhinitis. *Clin Exper Allergy* 2000;**30**:663-9.
40. Wilson N, Pedersen S. Inflammatory markers in clinical practice. *Am J Respir Crit Care Med* 2000;**162**:S48-51.
41. Koller DY, Herouy Y, Gotz M, Hagel E, Urbanek R, Eichller I. Clinical value of monitoring eosinophil activity in asthma. *Arch Dis Child* 1995;**73**:413-7.
42. Demoly P, Bousquet PJ. Links between allergic rhinitis and asthma still reinforced. *Allergy* 2008;**63**:251-4.
43. Dahl R, Venge P. Blood eosinophil leucicyte and eosinophil cationic protein: in vivo study of the influence of beta-2-adrenergic drugs and steroid medication. *Scand J Respir Dis* 1978;**59**:319-22.
44. Badr El Din OM, El Sawy IH, El Azzouni OE, Badr El Din MMA, Salem AM. Eosinophilic cationic protein as a serological markers of disease activity in childhood bronchial asthma. *East Med Health J* 1999;**5**:664-76.
45. Ferguson AC. Evaluation of serum ECP as marker of disease activity in chronic asthma. *J Allergy Clin Immunol* 1995;**95**:23-8.
46. Niimi A, Amitani R, Suzuki K, Tanaka E, Murayama T, Kuze F. Serum eosinophil cationic protein as a marker of eosinophilic inflammation in asthma. *Clin Exp Allergy* 1998;**28**:233-40.
47. Zimmerman B. Total blood eosinophil, serum ECP, and EPX in childhood asthma: reaction to disease status and therapy. *Clin Exp Allergy* 1993;**23**:564-70.
48. Sugai T, Sakiyama Y, Matumoto S. Eosinophil cationic protein in peripheral blood of pediatric patients with allergic diseases. *Clin Exp Allergy* 1992;**22**:275-81.
49. Cha YJ, Chae SL, Chang EA. Serum ECP levels in patients with allergic diseases. *Korean J Clin Pathol* 1999; **19**:348-52.
50. Kovacevic S, Bogic M, Peric-Popadic A, Jovicic Z, Raskovic S, Stehanovic LJ. The influence of atopic constitution, the severity, and exacerbation of the disease on serum ECP concentration in patients with bronchial asthma. *Allergy* 2003;**58**:1079-81.
51. Katsoulis K, Kontakiotis T, Leonardopoulos I, Kotsovili A, Legakis IN, Patakas D. Serum total antioxidant status in severe exacerbation of asthma, correlation with severity of the disease. *J Asthma* 2003;**40**:847-54.
52. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxiudative stress in asthma. *Am J Respir Crit Care Med* 1996;**154**:1055-60.
53. Akbay E, Arbaq H, Uyar Y, Ozturk K. [Oxidative stress and antioxidant factors in pathophysiology of allergic rhinitis]. *Kulak Burun Bogaz Ihtis Derg* 2007;**17**:189-96 (in Turkey).
54. Ozarus R, Tahan V, Turkmen S *et al*. Changes in malodialdehyde levels in bronchoalveolar fluid and serum by the treatment of asthma with inhaled steroid and beta-2-agonist. *Respirology* 2000;**5**:289-92.
55. Nadeem A, Chhabra SK, Masood A *et al*. Increased oxidative stress and altered levels of of antioxidants in asthma. *J Allergy Clin Immunol* 2003;**111**:72-8.
56. Mihmanli A, Guneylioglu D, Ozseker F, Arslan S, Ozgel E. Astimili hastalarda serbest oksijen radikalleri ve antioksidanlarin aktiviteleri. *Toaks Dergisi* 2003;**4**:264-8 (in Turkey).
57. Melen E, Bruce S, Doekes G *et al*. Haplotypes of G protein-coupled receptor 154 are associated with childhood allergy and asthma. *Am J Respir Crit Care Med* 2005; **171**:1089-95.
58. Togias A. Systemic effects of local allergic diseases. *J Allergy Clin Immunol* 2004;**113** (Suppl 1):S8-14.