

# Risk Factors for Asthma in Patients with Pollen Allergic Persistent Rhinitis

## *Polen Alerjik Persistan Rinitli Hastalarda Astım Gelişimi İçin Risk Faktörleri*

Ali Kutlu,<sup>1</sup> M.D, Bülent Bozkurt,<sup>1</sup> M.D., Ogün Sezer,<sup>2</sup> M.D., Oktay Taskapan,<sup>1</sup> M.D.

### BACKGROUND

Even though not a life-threatening disease, pollen allergic rhinitis (AR) has a remarkable social impact and cannot be left to its natural course. Pollens appear seasonally and are reflected in the symptoms of patients with AR living in temperate climates as in Turkey. Our aim was to determine prospectively the clinical characteristics of the patients diagnosed with pollen allergic persistent rhinitis and their risk factors for asthma in our allergy clinic.

### METHODS

A prospective study was conducted among 102 pollen AR patients with persistent symptoms in GATA Haydarpaşa Hospital, Department of Allergy, between March 2005-September 2006. Participants were evaluated for allergic respiratory diseases, then were skin tested using the prick test method. A serum sample was analyzed for total IgE and peripheral blood eosinophil counts.

### RESULTS

The mean age of the patients was 30.64±7.9 years and 69.6% were male. The most accompanying sensitivity was against house dust mites (62.7%). Monosensitization was found to be protective factor for the development of moderate-severe disease. The common accompanying allergic disease, asthma, was observed in 46 (45.1%) of the patients, 13 of whom had positive family history of asthma. IgE levels and total eosinophil counts were significantly higher in the non-asthmatic patients.

### CONCLUSIONS

Patients with AR were admitted to allergy clinics quite late, especially when persistent symptoms emerged. This might be due to AR not being considered as a serious disease. High IgE level and/or total eosinophil count were found to be protective factors for the development of asthma.

Key words: Asthma; persistent rhinitis; pollen; risk factors.

### AMAÇ

Her ne kadar hayatı tehdit eden bir hastalık olmasada, polen alerjik rinitin (AR) sosyal hayat üzerine belirgin etkileri vardır ve kendi seyrine bırakılamaz. Polenler mevsimsel olarak ortaya çıkmakta ve ılıman iklimde bulunan ülkemizde yaşayan AR'li hastalarda semptomlara yol açmaktadır. Bu çalışmada, polen alerjik persistan rinit tanısı konulan hastaların klinik karakteristik özelliklerini ve astım gelişimi için risk faktörlerini prospektif olarak belirledik.

### YÖNTEM

Bu prospektif çalışma Mart 2005-Eylül 2006 tarihleri arasında GATA Haydarpaşa Alerjik Hastalıklar Servisine müracet eden persistan semptomları olan 102 polen AR'li hasta ile yürütüldü. Çalışmaya alınan hastalar alerjik solunumsal hastalıklar açısından değerlendirildi, prick test yöntemiyle deri testleri yapıldı. Serum örnekleri total IgE ve periferik eozinofil sayısı ölçümü için analiz edildi.

### BULGULAR

Hastaların ortalama yaşı 30.64±7.9 yıl olup, %69.6'sı erkektir. Polen alerjisine en sık ev tozu akarlarına karşı duyarlanma (%62.7) eşlik etmektedir. Orta-şiddetli hastalık gelişimi için monosensitizasyon koruyucu faktör olarak bulunmuştur. AR'ye 46 (%45.1) hastada astım eşlik etmekte olup bu hastaların 13'ü astım için pozitif aile öyküsüne sahiptir. Non-astımlı grupta total eozinofil sayısı ve IgE seviyesi anlamlı olarak yüksekti.

### SONUÇ

AR'li hastalar alerji kliniklerine oldukça geç, özellikle persistan semptomlar ortaya çıkınca başvurmaktadır. Bu AR'nin ciddi bir hastalık olarak kabul edilmemesinden kaynaklanabilir. Yüksek IgE ve total eozinofil sayısını astım gelişimi için koruyucu faktör olarak bulunmuştur.

Anahtar sözcükler: Astım; persistan rinit; polen; risk faktörleri.

Allergic diseases have already become a major public health problem in many industrialized countries, not least in children and adolescents, and there is considerable evidence that the prevalence of allergic diseases is increasing worldwide. Recent studies suggest that 25% of the European population suffers from allergies.<sup>(1-4)</sup> The allergic response in sensitized individuals is mediated by IgE-dependent mechanisms. After sensitization of susceptible individuals and the synthesis of allergen specific IgE, atopic individuals respond to environmental allergens with a type I hypersensitivity reaction. Among these allergens, grass pollens affect nearly 20% of the European population and reveals, in sensitive patients, symptoms of rhinitis, conjunctivitis and/or bronchial asthma.

Allergic rhinitis (AR), a chronic disorder of nose and sometimes airways, is one of the most commonly seen allergic diseases, which is totally IgE-mediated. Allergic rhinitis which is generally characterized by nasal obstruction, rhinorrhea, sneezing, itching of the nose and/or postnasal drainage is often associated with respiratory and ocular symptoms. The association between rhinitis and conjunctivitis is a typical feature of patients with seasonal pollen allergy. However, conjunctival symptoms are often considered to be of minor importance and possibly not spontaneously reported by patients with rhinitis and/or asthma during medical interviews or in questionnaire-based studies such as the ISAAC and the ECRHS.<sup>(5,6)</sup> The perennial allergic rhinitis and seasonal allergic rhinitis are now respectively referred to as ‘persistent’ and ‘intermittent’ allergic rhinitis.<sup>(7)</sup> The association between exposure to environmental allergens and symptoms is relatively easily established in intermittent allergic rhinitis, where there is a marked contrast in symptom severity in and out of the pollen season. In persistent allergic rhinitis, however, the predominant allergen is house dust mite (HDM), which has little or no seasonal variation. The lack of a distinct contrast between symptomatic and asymptomatic periods makes it difficult to clearly recognize the relation to allergy.<sup>(8)</sup>

In pollen allergy, allergen exposure may lead to symptoms of rhinitis followed, in a few years time, by asthmatic symptoms (“an allergy march”). AR is a known risk factor for developing

of asthma;<sup>(9-11)</sup> furthermore, it affects individuals during their most productive years of childhood and young adulthood<sup>(12)</sup> and has a substantial negative impact on quality of life.

Although asthma and rhinitis often occur together, the reason for this common comorbidity is still a matter of debate. On the one hand, asthma and rhinitis might be different manifestations of the same atopic disease. On the other hand, asthma and rhinitis might interact with each other. Upper and lower airways might be influenced by a common inflammatory process, which might be sustained and amplified by intertwined mechanisms. The same inflammatory cells (T cells, eosinophils) and TH2-like cytokines have been found in nasal and bronchial biopsy specimens. It has recently been shown that segmental bronchial provocation might induce nasal inflammation in patients with allergic rhinitis, and that, conversely, nasal allergen provocation might induce inflammation in the bronchial epithelium.<sup>(13)</sup>

The capacity of pollen sensitizing the patients is theoretically universal, but the nature and number of pollen vary with geography, temperature and climate. The pollen concentration in the atmosphere depends on the vegetation and climate of a given geographic zone causing important regional differences. The main cause of allergic rhinitis in Turkey seems to be grass pollen sensitivity according to recent studies.<sup>(14-18)</sup>

It is a highly prevalent condition that exacts a high cost in terms of morbidity, loss of productivity, and use of healthcare resources. Despite the recognition that AR is a global health problem affecting up to 40% of the population worldwide and is increasing in prevalence, there are insufficient epidemiological data with regard to its clinical features and treatment trends in our country.<sup>(19-21)</sup>

Various recent studies in children and university students from different parts of Turkey show an allergic rhinitis prevalence of 9.1-13.6%, which is lower than the prevalence in western countries.<sup>(14,15,22,23)</sup>

Our aim was to determine prospectively the clinical characteristics of the patients diagnosed with pollen allergic persistent rhinitis and risk factors for asthma in our allergy clinic.

## METHODS

### Patients

A prospective study was conducted among 102 pollen allergic rhinitis patients with persistent symptoms admitted to our clinic in GATA Haydarpasa Hospital, Department of Allergy, between March 2005 and September 2006. All subjects were included over the pollen and mite seasons to overcome the possible seasonal differences in symptoms and test solutions. The rhinitis symptoms of nasal obstruction, itching/sneezing and secretion/runny nose were each scored separately on a severity scale between 0 and 3 (0= absent, 1 = mild, 2 = moderate and 3 = severe). These three symptom scores were combined to produce total nasal symptom score (TNSS) with a maximum score of 9. This TNSS was used in our analysis. The questions asked by same allergist that made up the TNSS were as follows:

Rate the following symptom:

Was it

0= no symptom;

1= mild - awareness but not troubled;

2= moderate - troublesome but not interfering with normal daily activities or sleep;

3= severe - interfering with normal daily activities or sleep.

### Skin Tests

Participants were evaluated for allergic respiratory diseases (asthma and rhinitis) and then were skin tested using the prick test method with a lancet. A standardized panel (ALK, Denmark) including house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinea*), mold, grass, tree, weed, feather and dander mix antigens were applied accompanied by positive (0.1% histamine phosphate) and negative (serum physiologic: phosphate-buffered physiologic saline) controls.<sup>(24)</sup> Resulting wheals were measured after 15 min. A positive reaction was defined as a wheal with a geometric mean diameter of at least 3 mm. Prick test positivity was defined as a positive response to at least one of the allergens used. Prick tests were not performed in cases of pregnancy, dermographism and use of antihistamines. Antihistamines were withheld 7 days before skin testing. All subjects

signed informed consent forms before participating.

### In Vitro Tests

A serum sample drawn was analyzed for total IgE on admission. Total IgE was determined by using the microparticle enzyme immunoassay on the Imx analyzer (Abbott park, IL, USA), according to the manufacturer's instructions. Peripheral blood eosinophil counts were estimated microscopically and were expressed as number of cells per microliter. Peripheral blood eosinophilia was defined as >200 cells/ml.

### Statistical Analysis

Statistical analyses were performed by using SPSS 11.00 for Windows statistical software. Personal characteristics and disease-related factors were compared between asthma and allergic rhinitis.  $\chi^2$  testing with continuity correction and student's t test were used for categorical and continuous variables, respectively. Association of the factors with asthma was adjusted for age and gender. Odds ratios were used to assess the strength of the association between asthma and characteristics of the patients. A final logistic regression model was developed to assess the independent association between asthma and the factors which were significantly associated with asthma in the adjusted analysis. Model selection criteria were 0.05 and 0.10 for entry and removal of the factors, respectively. Statistical significance was defined for p values less than 0.05.

**Table 1.** The Clinical Characteristics of the Patients with Pollen Allergic Persistent Rhinitis (n=102).

Gender (Male)	71 (69.6%)
Age (mean±SD)	30.64±7.9
Duration of disease (yrs)	11.1±7.7
Familial atopy	51 (50.0%)
Familial asthma	13 (12.7%)
Total IgE (mean±SD)	291±304.6
Total eosinophil count	364.6±304.2
Bronchial asthma n (%)	46 (45.1%)
Moderate- severe rhinitis	74 (72.5%)
Polysensitization	100 (98%)

**Table 2.** The Severity of Nasal Symptoms on Symptom Basis.

	No symptom	Mild	Moderate	Severe
Nasal secretion (Runny nose)	1 (1%)	13 (12.7%)	30 (29.4%)	58 (56.9%)
Nasal itching / Sneezing	4 (3.9%)	16 (15.7%)	34 (33.3%)	48 (47.1%)
Nasal obstruction	1 (1%)	9 (8.8%)	47 (46.1%)	45 (44.1%)

## RESULTS

The mean age of the patients was 30.6±7.9 years and 69.6% were male (Table 1). Almost all of the patients had several grade of nasal symptoms as runny nose, nasal itching/sneezing, nasal obstruction (Table 2). Skin prick tests were positive in all of patients for pollens, where the most accompanying sensitivity was against house dust mites (either *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*) (62.7%) (Table 3). The mean duration of the disease was 11.1±7.7 years. The mean total IgE level of patients was 291±304.6 U/ml. The mean total eosinophil count of patients was 364.6±304.2 cells/µl. Among the patients with persistent allergic rhinitis; 26.5% of patients had mild, 73.5% of patients had moderate-severe disease. Monosensitization was found to be protective factor for the development of moderate-severe disease (Table 4). The commonly accompanying allergic disease, bronchial asthma, was observed in 46 (45.1%) of the patients, 13 of whom had positive family history of asthma. The half of patients had history of familial atopy. The higher total IgE levels and total eosinophil counts were significantly found protective for the asthmatic patients (Table 5).

## DISCUSSION

Even though not a life-threatening disease, AR has a remarkable social impact and can not be left to its natural course. Pollens appear seasonally and are reflected in the symptoms of patients with AR living in temperate climates. Recent studies have shown that grass pollens affect nearly 20% of the European population.

Although AR is known to be a disease of younger age groups, the onset was quite late with a mean age at onset of 30.6 compared to western

**Table 3.** The Allergen Spectrum of the Patients with Pollen Allergic Persistent Rhinitis (n=102).

Aeroallergens	n (%)
Pollen sensitivity	Grass 100 (98.0%)
	Tree 85 (83.3%)
	Weed 60 (58.8%)
Mite sensitivity	64 (62.7%)
Dander sensitivity	48 (47.1%)
Mold sensitivity	34 (33.3%)
Feather sensitivity	11 (10.8%)

**Table 4.** Association Between Severity of Rhinitis Combined with Allergic Rhinitis and Patient Characteristics and Disease Related Factors Adjusted for Age and Gender.

Potential risk factors	Adjusted OR (95% CI)
<b>For moderate- severe rhinitis</b>	
Bronchial asthma	N/A
Familial atopy	N/A
Familial asthma	N/A
Moderate- severe rhinitis	N/A
High TNSS	N/A
Long duration of disease (>3 years)	N/A
Total IgE (>200 U/ml)	N/A
Total eosinophil count (>200 cells/µl)	N/A
Grass pollen sensitivity	N/A
Tree pollen sensitivity	N/A
Weed pollen sensitivity	N/A
Mite sensitivity	N/A
Dander sensitivity	N/A
Mold sensitivity	N/A
Feather sensitivity	N/A
Monosensitization	0.26 (0.21-1.45)**

\*p<0.05; \*\* p<0.01; \*\*\* p<0.005; \*\*\*\* p 0.0001; N/A: Not available.

**Table 5.** Association Between Asthma Combined with Allergic Rhinitis and Patient Characteristics and Disease Related Factors Adjusted for Age and Gender.

Potential risk factors	Adjusted OR (95% CI)	Final model OR (95% CI)
Familial atopy	N/A	N/A
Familial asthma	N/A	N/A
Moderate- severe rhinitis	N/A	N/A
High TNSS	N/A	N/A
Long duration of disease (>3 yrs)	0.24 (0.03-0.59)*	N/A
Total IgE (>200 U/ml)	0.32 (0.12-0.52)***	0.34 (0.12-0.56)***
Total eosinophil count (>200 cells/ $\mu$ l)	0.32 (0.11-0.54)***	0.28 (0.06-0.51)*
Grass pollen sensitivity	N/A	N/A
Tree pollen sensitivity	N/A	N/A
Weed pollen sensitivity	N/A	N/A
Mite sensitivity	N/A	N/A
Dander sensitivity	N/A	N/A
Mold sensitivity	N/A	N/A
Feather sensitivity	N/A	N/A
Monosensitization	N/A	N/A

\* p<0.05; \*\* p<0.01; \*\*\* p<0.005; \*\*\*\* p<0.0001; N/A: Not available.

countries where the onset of AR is before the age of 15 years.<sup>(19-21)</sup> This might be explained by regional variations in the pollen type and concentrations and lifestyle without considering AR as a serious disease. Although no significant difference in gender was reported in patients with AR in previous epidemiological studies worldwide, 69.6% of our patients were male. There has been no clear data on this up to date.

According to ARIA classification; the patients with allergic rhinitis were classified as ‘persistent’ and ‘intermittent’ allergic rhinitis instead of perennial and seasonal allergic rhinitis.<sup>(7)</sup> The association between exposure to environmental allergens “mainly pollens” and symptoms is relatively easily established in intermittent allergic rhinitis. However, on recent publications, the predominant allergen was shown to be house dust mite in persistent allergic rhinitis, which had little or no seasonal variation. Furthermore, recent studies show that a significant inflammatory reaction was evident throughout the pollen season, even during the days with a low pollen count and low or absent symptoms.<sup>(25,26)</sup> This is the first study on clinical

characteristics of patients with persistent allergic rhinitis having pollen hypersensitivity.

In addition to this classification; the gradation of the severity of AR in our patients were classified into two groups was made depending on the symptom severity; mild allergic rhinitis and moderate-severe allergic rhinitis. In our study, the three-fourth of the patients had moderate-severe allergic rhinitis. Among examined all other factors, only monosensitization was found to be protective (Table 4). Most patients were polysensitized. Thus, it appears that the ARIA classification appears to be more appropriate than the older one as it confirms the reasons explaining why the classification had to be changed.

Allergy does not necessarily limit itself to the nose. The nose and/or conjunctiva are probably the most commonly involved organs in pollen AR which can be accepted as a systemic disease. In addition, the high frequency of accompanying allergic asthma with a percentage of 45.1% points to the need that at least the initial evaluation of AR patients should be done at allergy clinics. Asthma and AR frequently appear as comorbid

conditions. Although asthma and rhinitis often occur together, the reason for this common comorbidity is still a matter of debate. On the one hand, asthma and rhinitis might be different manifestations of the same atopic disease. On the other hand, asthma and rhinitis might interact with each other. Upper and lower airways might be influenced by a common inflammatory process, which might be sustained and amplified by intertwined mechanisms. The same inflammatory cells (T cells, eosinophils) and TH2-like cytokines have been found in nasal and bronchial biopsy specimens. It has recently been shown that segmental bronchial provocation might induce nasal inflammation in patients with allergic rhinitis, and that, conversely, nasal allergen provocation might induce inflammation in the bronchial epithelium. Although there are various studies on asthma risk factors among children and adults with rhinitis, the factors which are involved in the development of pollen allergic rhinitis into asthma are still not clear.<sup>(27)</sup> Contrary to the previous studies where high IgE level, long rhinitis duration had shown to be a predictor of asthma- rhinitis connection,<sup>(28,29)</sup>

analysis of our data suggested long duration of symptoms of rhinitis, high total IgE and eosinophil levels as protective factors for the development of asthma in patients with pollen allergic persistent rhinitis. However, a seasonal increase of serum total IgE levels which can be observed in patients with pollen allergy might affect our study as a seasonal confounding factor.<sup>(30)</sup> The analysis of eosinophilia in the general population was able to reveal potential allergic patients and potential allergic diseases.<sup>(31)</sup> However, this was a cross-sectional study and it is not possible to assess the temporal association and causality of the associations.

In conclusion, AR patients were admitted to allergy clinics quite late, only when persistent symptoms emerged. This might be due to SR not being considered as a serious disease. High total IgE level and/or total eosinophil count were found to be protective for the development of asthma. As this study was across-sectional study, large, detailed and prospective community-based studies are needed in order to clarify asthma- rhinitis connection.

## REFERENCES

1. Lundbäck B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998;28 Suppl 2:3-10.
2. de Monchy J, Andersen PS, Bergmann KC, Chivato T, Holm-Hansen A, Jarisch R, et al. Living & learning with allergy: a European perception study on respiratory allergic disorders. *Respir Med* 2004;98:404-12.
3. Wozczek G, Kowalski ML, Borowiec M. Association of asthma and total IgE levels with human leucocyte antigen-DR in patients with grass allergy. *Eur Respir J* 2002;20:79-85.
4. Wilson AM, Duong M, Crawford L, Denburg J. An evaluation of peripheral blood eosinophil/basophil progenitors following nasal allergen challenge in patients with allergic rhinitis. *Clin Exp Allergy* 2005;35:39-44.
5. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
6. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
7. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):S147-334.
8. Van Hoescke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. *Allergy* 2006;61:705-11.
9. Ulrik CS, Backer V, Hesse B, Dirksen A. Risk factors for development of asthma in children and adolescents: findings from a longitudinal population study. *Respir Med* 1996;90:623-30.
10. Yin J, Yue FM, Wang LL, He HJ, Xu T, Li H, et al. Natural course from rhinitis to asthma in the patients with autumnal pollinosis: a clinical study of 1096 patients. [Article in Chinese] *Zhonghua Yi Xue Za Zhi* 2006;86:1628-32. [Abstract]
11. Settapanne RJ, Settapanne GA. IgE and the allergy-asthma connection in the 23-year follow-up of Brown University students. *Allergy Asthma Proc* 2000;21:221-5.
12. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94(6 Pt 1):895-901.
13. Passalacqua G, Guerra L, Licenziato M, et al. Asthma-rhinitis comorbidity. *Allergy Clin Immunol Int* 2003;15:105-9.
14. Kalyoncu AF. Perennial and seasonal rhinitis in Ankara, Turkey. *Allergy* 1997;52:1040-1.
15. Bostanci L, Türktas I, Türkyılmaz C. Sensitization to aeroallergens in Ankara, Turkey. *Allergy* 1999;54:1332-4.
16. Harmanci E, Metintas E. The type of sensitization to pollens in allergic patients in Eskisehir (Anatolia), Turkey. *Allergol Immunopathol (Madr)* 2000;28:63-6.
17. Erel F, Karayavaz M, Caliskaner Z, Ozangüç N. The allergen spectrum in Turkey and the relationships between allergens and age, sex, birth month, birthplace, blood groups and family history of atopy. *J Invest Allergol Clin Immunol* 1998;8:226-33.
18. Akçakaya N, Kulak K, Hassanzadeh A, Camcioğlu Y, Cokuğraş H. Prevalence of bronchial asthma and allergic rhinitis in Istanbul school children. *Eur J Epidemiol* 2000;16:693-9.

19. Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99(6 Pt 2):S805-28.
20. van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. *European Academy of Allergology and Clinical Immunology. Allergy* 2000;55:116-34.
21. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations 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.
22. Celik G, Mungan D, Bavbek S, Sin B, Ediger D, Demirel Y, et al. The prevalence of allergic diseases and atopy in Ankara, Turkey: a two-step population-based epidemiological study. *J Asthma* 1999;36:281-90.
23. Kalyoncu AF, Demir AU, Ozcakar B, Bozkurt B, Artvinli M. Asthma and allergy in Turkish university students: Two cross-sectional surveys 5 years apart. *Allergol Immunopathol (Madr)* 2001;29:264-71.
24. Osterballe O, Weeke B. A new lancet for skin prick testing. *Allergy* 1979;34:209-12.
25. Liccardi G, Kordash TR, Russo M, Noschese P, Califano C, D'Amato M, et al. Why are nasal and bronchial symptoms mostly perennial in patients with monosensitization to *Olea europaea* pollen allergens? *J Investig Allergol Clin Immunol* 1996;6:371-7.
26. Ricca V, Landi M, Ferrero P, Bairo A, Tazzer C, Canonica GW, et al. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;105(1 Pt 1):54-7.
27. Settipane RJ, Settipane GA. IgE and the allergy-asthma connection in the 23-year follow-up of Brown University students. *Allergy Asthma Proc* 2000;21:221-5.
28. Beech KM, Beier J, Buhl R. Seasonal variations of serum-IgE and potential impact on dose-calculation of omalizumab (rhuMab-E25, anti-IgE). [Article in German] *Pneumologie* 2004;58:546-51. [Abstract]
29. Staikuniene J, Sakalauskas R. The immunological parameters and risk factors for pollen-induced allergic rhinitis and asthma. [Article in Lithuanian] *Medicina (Kaunas)* 2003;39:244-53. [Abstract]
30. Sin BA, Inceoglu O, Mungan D, Celik G, Kaplan A, Misirligil Z. Is it important to perform pollen skin prick tests in the season? *Ann Allergy Asthma Immunol* 2001;86:382-6.
31. Laaidi K, Besancenot JP, Carli PM. Evolution of eosinophilia during the pollen season among the general population: a way of determining new sensitizations. [Article in French] *Allerg Immunol (Paris)* 2002;34:13-8. [Abstract]