

High prevalence and young onset of allergic rhinitis in children with bronchial asthma

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Bronchial asthma and allergic rhinitis often co-exist, and rhinitis is a major risk factor for the development of asthma. However, the reported incidence of allergic rhinitis in asthmatic children varies widely. The aim of this study was to elucidate the incidence of allergic rhinitis, the onset age of chronic upper and lower airway symptoms, and the correlation of these two symptoms in asthmatic children. A cohort of 130 consecutive children (ages 2–10) with asthma was evaluated. A questionnaire regarding upper and lower airway symptoms was filled out by the parents. Objective diagnosis of allergic rhinitis was also made on the basis of rhinoscopy, nasal cytology, nasal challenge, and specific serum IgE (CAP-RAST). Persistent nasal symptoms were present in 83.8% of the asthmatic children. The incidence of allergic rhinitis was 77.7% based on the objective findings. The mean onset age of asthma was 2.8 yr, and that of rhinitis was 2.9 yr. Nasal symptoms started as early as the first year of life in 8.9% of the children. In children with comorbid asthma and allergic rhinitis, rhinitis preceded in 33.7%, asthma preceded in 31.7%, and both started in the same year in 26.7%. In 7.9%, rhinitis was asymptomatic. Concomitant exacerbation of the upper and lower airways occurred in 34.6% of the total 130 children. These results demonstrate that allergic rhinitis manifested early in life in the majority of the asthmatic children. Persistent nasal symptoms in infancy may point to subsequent development of asthma and possible early intervention.

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Prevalence of allergic diseases in children is increasing (1, 2) and it is widely accepted that allergic rhinitis and bronchial asthma commonly occur together. However, the reported prevalence of allergic rhinitis in patients with asthma, which is mostly based on a questionnaire to the patients, ranges from 6.2% to 95% (3). This wide variability may be attributed to the fact that there is no standardized questionnaire for the diagnosis of rhinitis and that patients with rhinitis and asthma often 'ignore' their upper respiratory symptoms because of their more prominent lower airway symptoms (3). Defining 'allergic' nasal symptoms in children is even more

difficult because of the high frequency of upper respiratory infections in early childhood. In addition, young children rarely complain of nasal symptoms. To overcome the limitation of the questionnaire method, we performed objective diagnosis of allergic rhinitis based on the nasal endoscopy, nasal cytology, nasal provocation test, and serum specific IgE in a cohort of children with asthma. This approach enabled us to effectively utilize a questionnaire and to identify true prevalence of allergic rhinitis in a defined population of childhood asthma.

Here, we found that the majority of children with asthma at a mean age of 5 yr also had

allergic rhinitis and that the onset of allergic rhinitis occurred relatively early in life, either concurrently or prior to asthma, in 60% of the patients.

Subjects and methods

We evaluated a cohort of children < 10 yr of age with atopic bronchial asthma who visited Mie National Hospital's pediatric allergy clinic during consecutive 12 months. We included only the pre-pubertal children because natural outgrowth of asthma often seen in adolescent age may confound the analysis of the two comorbid disorders. The diagnosis of atopic asthma was confirmed on the basis of a history of recurrent wheeze and dyspnea, reversible bronchoconstriction, and sensitivity to at least one inhalant allergen as evidenced by a positive CAP-RAST. One-hundred and thirty children (86 boys, 44 girls, ages 2–10; mean: 5.3 yr) who consecutively visited our clinic were enrolled in the study. Classification of the cases according to the international guideline (4) showed 77.9% as mild persistent, 18.6% as moderate persistent, and 3.5% as severe persistent asthma. Informed consent was obtained from the parents of the patients. All the children were found to be sensitized at least to house dust mite (HDM).

A questionnaire was filled out by the parents. It included questions concerning nasal symptoms, onset ages of rhinitis and bronchial asthma, correlation between nasal symptoms and asthma symptoms, and family history of allergic diseases. The parents were also asked whether a physician had ever diagnosed the nasal symptoms as being due to allergies. 'Persistent nasal symptoms' was defined on the basis of a positive answer to the following question: 'Has your child had a long-lasting runny or stuffy nose or episodes of sneezing, apart from colds?' Those who answered 'yes' were asked about the age when the problem started.

After the questionnaire, rhinoscopy, nasal cytology, and allergen provocation tests were performed. The diagnosis of HDM-sensitized allergic rhinitis was based on (i) presence of eosinophils in nasal smears; (ii) positive nasal provocation test with a HDM allergen disc; and (iii) positive specific serum IgE to HDM by CAP-RAST. The children who had at least two positive factors of the criteria were confirmed as allergic rhinitis. Because HDM is the most prevalent inhalant allergen and the majority of patients with perennial allergic rhinitis are sensitized to HDM in Japan (5, 6), the criteria covers most of perennial allergic rhinitis in the country.

Although Japanese cedar pollen (JCP) is the major allergen to cause 'seasonal' allergic rhinitis in Japan (7, 8), it does not relate to asthma prevalence (9) and we focused on HDM, not JCP, in this study.

The severity of rhinitis symptoms was determined according to the Japanese practice guideline for nasal allergy (10). In brief, the severity of nasal congestion was classified into four grades, i.e., no congestion was 'none,' congestion of one side was 'mild,' occasional congestion of both sides was 'moderate,' and complete congestion was 'severe.' The severity of rhinorrhea and sneezing was also classified into four grades on the basis of the number of nose blows and sneezes per day, i.e., <1 was 'none,' 1–5 was 'mild,' 6–10 was 'moderate' and >10 was 'severe.' The severity of rhinitis was assigned to that of the highest grade in any of the symptoms.

The chi-squared test was used to compare proportions of the data in different groups. A difference in percentages was considered significant when the p-value was <0.05.

Results

Previous diagnosis of allergic rhinitis

The parents of 75 children (57.7%) answered that their children had been diagnosed as having allergic rhinitis by another physician. In addition, the parents of 11 children thought that their children had had allergic rhinitis although a definitive diagnosis had never been made.

Prevalence and severity of persistent nasal symptoms based on the questionnaire

The replies to the questionnaire revealed that 109 children (83.8%) had had persistent nasal symptoms. The symptoms were mild in 26.9%, moderate in 40.0% and severe in 16.9% of the children. The combined ratio of 'severe' and 'moderate' symptoms was 50.4% for nasal congestion, 23.1% for rhinorrhea and 10.7% for sneezing. Concerning other symptoms, 22.3% of the 130 children had recurrent epistaxis, 46.2% had frequent sniffing, 30.0% had snoring, 40.8% had a cough, and 32.3% had eye symptoms.

Prevalence of allergic rhinitis based on objective findings

Rhinoscopy and nasal cytology were performed in all the children. Eosinophilia in nasal smears was positive in 97 (74.6%) of them. Nasal provocation tests were positive in 45 (84.9%) of 53 children who could be carried out the test.

Seventy-seven children were unable to be performed the test because they were too young. On the basis of the diagnostic criteria, 101 children (77.7%) were confirmed as allergic rhinitis. All the children diagnosed as allergic rhinitis had pale or red swollen mucosa and/or watery discharge with rhinoscopy. Twenty-seven (26.7% of 101 children) had mild, 42 (41.6%) had moderate, and 20 (19.8%) had severe nasal symptoms.

Table 1 summarizes the relationship between prevalence of persistent nasal symptoms found by the questionnaire and objective diagnosis of allergic rhinitis. Positive predictive value for the questionnaire was 81.7% and negative predictive value was 42.9%. Actually, the parents of 12 (11.9% of total subjects) children had not noticed any nasal symptoms in their children despite the presence of typical mucosal findings of allergic rhinitis. Twenty-nine (22.3% of total subjects) children did not have objective findings of allergic rhinitis, although the parents of 20 children complained of persistent nasal symptoms in their children. Six of those 20 children were diagnosed as having sinusitis.

Age at onset of asthma and rhinitis symptoms

As presented in Fig. 1, the distributions of the onset ages of asthma and rhinitis were similar. The mean onset age of asthma in all the patients was 2.8 ± 1.9 yr. In 89 children with both asthma and symptomatic allergic rhinitis, nasal symptoms started at 2.9 ± 1.7 yr of age. In children with allergic rhinitis, nasal symptoms started as early as the first year of life in 9.0% of them and at 2 yr of age in 22.5%. In the patients who were previously diagnosed as having allergic rhinitis by other physicians, the mean age at the diagnosis was 3.5 ± 1.7 yr.

Table 1. Prevalence of allergic rhinitis based on objective findings and persistent nasal symptoms found by the questionnaire

	Persistent nasal symptoms found by the questionnaire		
	+	-	
Allergic rhinitis			
+	89*	12	101 (77.7%)
-	20†	9	29 (22.3%)
Total	109 (83.8%)	21 (16.2%)	130

Positive predictive value and negative predictive value for the questionnaire were 81.7% and 42.9%, respectively.

*Twenty-seven had mild, 42 had moderate, and 20 had severe nasal symptoms.

†Six of them were diagnosed as having sinusitis.

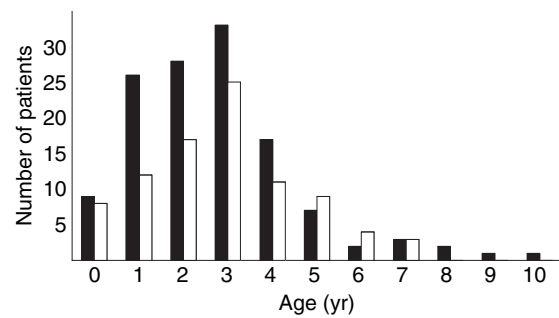


Fig. 1. Distribution of the age at onset of asthma and rhinitis symptoms. Closed bar: onset of bronchial asthma in total children ($n = 130$, 2.8 ± 1.9 yr). Open bar: onset of nasal symptoms in children with allergic rhinitis ($n = 89$, 2.9 ± 1.7 yr).

The children with asthma who also had allergic rhinitis were further subdivided into four groups according to which of the two illnesses started first. Of the 101 children who were diagnosed as having allergic rhinitis, the onset of asthma preceded in 32 (31.7%), the onset of rhinitis preceded in 34 (33.7%), and both diseases manifested at the same time in 27 (26.7%) patients. Eight (7.9%) patients had asymptomatic rhinitis. Table 2 summarizes the patients' current age and the age of onset of the illnesses. It is of note that the initial symptoms occurred at an age of 2 yr regardless of the airway site, and that allergic rhinitis started at a young age, either concurrently or prior to asthma, in 61 children (60.4%).

The correlation between upper respiratory symptoms and bronchial asthma

Concomitant exacerbation of the upper airways with the bronchial asthma occurred in 34.6% of the total 130 children. Concomitant exacerbation was experienced in 33.7% of the children with rhinitis. Interestingly, even in the case of children without evidence of rhinitis, 37.9% experienced nasal symptoms when their asthma exacerbated, which may indicate that viral upper respiratory infections had caused asthma exacerbation. Alternate exacerbations of the upper and lower airway symptoms were found only in one case (0.9%).

Family history of allergic diseases

The data on the family history of allergic diseases are shown in Fig. 2. A family history of bronchial asthma was seen significantly more frequently in children whose nasal symptoms started early, before the onset of asthma or at

Table 2. Current age and the onset age of bronchial asthma and nasal symptoms

Group (n)	Current age (mean $\pm$ 1 s.d.)	Sex (M/F)	Onset age (mean $\pm$ 1 s.d.)	
			Bronchial asthma	Nasal symptoms
Children without allergic rhinitis (asthma alone) (29)	4.2 $\pm$ 1.7	19/10	2.3 $\pm$ 1.3	—
Children with asthma and allergic rhinitis (101)				
Asthma preceded (32)	6.0 $\pm$ 2.1	24/8	2.1 $\pm$ 1.5	3.9 $\pm$ 1.5
Nasal symptoms preceded (34)	5.6 $\pm$ 2.4	21/13	4.2 $\pm$ 2.2	2.3 $\pm$ 1.6
Both symptoms occur at the same time (27)	4.8 $\pm$ 2.3	15/12	2.3 $\pm$ 1.6	2.3 $\pm$ 1.6
Asymptomatic rhinitis (8)	5.6 $\pm$ 2.5	7/1	2.0 $\pm$ 1.3	—

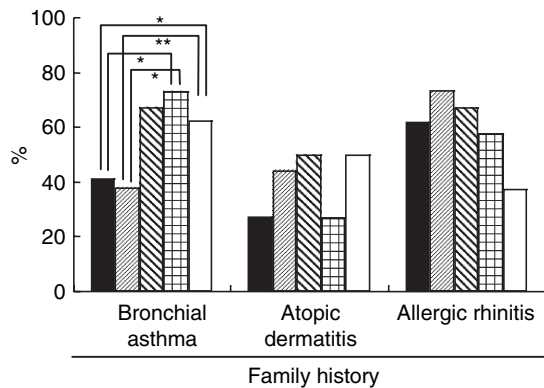


Fig. 2. The prevalence of family history of allergic disease. The patients were divided into the following groups on the basis of comorbidity of rhinitis and relative precedence of the onset: closed bar, asthma alone; Fine hatched bar, asthma preceded; large hatched bar, rhinitis preceded; cross striped bar, both symptoms occurred at the same time; open bar, asthma and asymptomatic rhinitis. * $p < 0.05$, ** $p < 0.01$. A family history of asthma was significantly more common in children whose nasal symptoms started early, before the onset of asthma or at the same time with asthma than in those who had asthma alone or rhinitis of later onset.

the same time as the asthma compared with in those who had asthma alone or allergic rhinitis of later onset. There were no statistically significant differences in the prevalence of a family history of atopic dermatitis and allergic rhinitis among the groups.

Discussion

In this study, we found a high incidence of allergic rhinitis, about 80%, in children with asthma at a mean age of 5 yr old. Because the incidence in previous reports varies widely, we employed direct examination to diagnose rhinitis objectively in a cohort of 130 asthma patients < 10 yr of age, all of who visited our pediatric allergy clinic consecutively within a certain period.

It is of note that no nasal symptoms were recognized by the parents of 11.9% of children

who had objective findings of rhinitis, which was also evidenced by low negative predictive value, 42.9%, of the questionnaire. These findings suggest that a certain population of asthmatic children without nasal symptoms may have allergic rhinitis. Nasal symptoms of young infants may be unrecognized by the parents, and careful examination is thus important; several reports, although they deal with adults, support this finding. Gaga et al. (11) reported that eosinophil infiltration was present in the nasal mucosa of asthmatic patients even in the absence of rhinitis. Some of the asthmatic patients who considered themselves free of nasal symptoms were demonstrated to have evidence of nasal airway disease (3).

Next, we found that the nasal symptoms in asthmatic children started early in life. Nasal symptoms occurred as early as in the first year of life in 9.0% of asthmatic children with allergic rhinitis, and the mean onset age of rhinitis was 2 yr. In addition, nasal symptoms preceded bronchial asthma in 33.7% of the children, and the two symptoms started at the same time in 26.7%. These results indicate that nasal symptoms start in infancy in a considerable number of asthmatic children. An epidemiological study (12) reported that children whose rhinitis began in the first year of life were more likely to have respiratory symptoms or asthma at age 6 than those without. Leynaert et al. (13) indicated that rhinitis that develops in the first year of life is an early manifestation of an atopic pre-disposition and a risk factor for asthma. A recent large survey for allergic rhinitis in pre-school children using ISAAC [The International Study of Asthma and Allergies in Childhood (14)] written questionnaire also revealed that rhinitis has a strong association with wheezing symptoms, asthma (15).

The present study also showed that one-third of asthmatic children experienced concomitant exacerbation of upper and lower airway symptoms, even those without objective findings of allergic rhinitis. 'Exacerbation of nasal

symptoms' includes not only allergic inflammation but also viral or bacterial infections, such as a common cold or sinusitis. This finding indicates that any nasal symptoms can pre-dispose to exacerbation of asthma.

The mechanisms that connect upper and lower airway allergies are under active investigation. Proposed pathogenetic mechanisms include a nasobronchial reflex, mouth breathing caused by nasal congestion, and pulmonary aspiration of nasal contents (16). In school age children, viruses were detected in 80% of reported episodes of asthma exacerbations (17). Upper airway rhinovirus infection is an important risk factor for asthma exacerbation through various pathophysiologies to cause allergic inflammation in the lower airway, such as ICAM-1 expression (18). It has also been demonstrated that rhinovirus could directly infect lower airways (19). 'Spreading' of allergic inflammation from the upper airway to the lower airway may be induced since local allergic sensitization causes systemic production of allergen-specific IgE and T cells are able to migrate from regional lymph nodes and 'home-in' on other tissues (20).

The 'Allergic Rhinitis and its Impact on Asthma' WHO guideline stresses that asthma and rhinitis should be considered to be 'one disease' to achieve better control of the common 'one airway' diseases (21). Accumulating evidence suggests that treating allergic rhinitis in patients with comorbid asthma reduces the airway hyperresponsiveness and improves lung functions (22–24). Recent studies have demonstrated the efficacy of early intervention for allergic rhinitis in asthmatic patients (25, 26). Corren et al. (27) in a large scale case-control study, showed that treatment of asthmatic patients who had allergic rhinitis with either nasal corticosteroids or second-generation antihistamines was associated with a significantly lower risk of asthma-related emergency room treatment and hospitalization.

In the present study, a family history of asthma was more common in children who had comorbid allergic rhinitis, especially in children who had earlier onset of nasal symptoms. This finding suggests that a genetic pre-disposition may have some impact on the development of allergic rhinitis in early childhood (28). One should also be aware of possible environmental risks for early onset of rhinitis since it has been reported that environmental tobacco smoke was strongly associated with an increased risk of developing allergic rhinitis at age one (29). We could not, however, found a positive correlation between smoking of parents and onset age of persistent

nasal symptoms probably because of small number of subjects. Particular attention should be paid to coexistent lower airway symptoms in young children with nasal symptoms. However, the ideal time for early intervention and the most effective treatment strategy remain unknown.

Possible shortcomings exist in this study. First, evaluation of symptoms with questionnaire is prone to recollection bias especially for the onset age of nasal symptoms. This inherent problem in questionnaire, however, may be less problematic in this study because we included young children with mean age of 5 yr and the parents of them would have better memory of toddler ages than those of adolescent or older counterparts would. Second, our diagnostic criteria for 'objective' allergic rhinitis were based on sensitization to a single allergen, HDM, and we may have missed patients with perennial allergic rhinitis who may have been sensitized to other inhalant allergen. However, as described in Subjects and methods, HDM is the most prevalent perennial allergen for both allergic rhinitis and asthma in Japan and sensitization to other allergens without HDM sensitization is very rare except for seasonal allergen, JCP (5, 6, 30).

In conclusion, we found that 77.7% of asthmatic children had allergic rhinitis, and their nasal symptoms started early in life. We reached a diagnosis of allergic rhinitis in young children based on the objective findings. As recognition of rhinitis symptoms in infancy is difficult even for mothers, our findings suggest the importance of careful nasal examination in young children with asthma. A correct diagnosis of allergic rhinitis may be one of the clues for early intervention in respiratory allergic disease in children.

References

1. HAKANSSON K, THOMSEN SF, ULRIC CS, PORSBJERG C, BACKER V. Increase in the prevalence of rhinitis among Danish children from 1986 to 2001. *Pediatr Allergy Immunol* 2007; 18: 154–9.
2. SHAMSSAIN M. Trends in the prevalence and severity of asthma, rhinitis and atopic eczema in 6- to 7- and 13- to 14-yr-old children from the north-east of England. *Pediatr Allergy Immunol* 2007; 18: 149–53.
3. TOGIAS A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; 111: 1171–83.
4. Global Strategy for Asthma Management and Prevention. 2006. Available at: <http://www.ginasthma.org>.
5. MASUDA S, TAKEUCHI K, YUTA A, OKAWA C, UKAI K, SAKAKURA Y. [Japanese cedar pollinosis in children in our allergy clinic]. *Arerugi* 1998; 47: 1182–9.
6. KUSUNOKI T, KOREMATSU S, HARAZAKI M, ITO M, HOSOI S. [Recent pollen sensitization and its possible involvement in allergic diseases among children in a pediatric allergy clinic]. *Arerugi* 1999; 48: 1166–71.

7. OKUBO K, OGINO S, NAGAKURA T, ISHIKAWA T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Allergol Int* 2006; 55: 379–86.
8. OZASA K, DEJIMA K, TAKENAKA H. Prevalence of Japanese cedar pollinosis among schoolchildren in Japan. *Int Arch Allergy Immunol* 2002; 128: 165–7.
9. KAGAMIMORI S, NARUSE Y, WATANABE M, NOHARA S, OKADA A. An epidemiological study on total and specific IgE levels in Japanese schoolchildren. *Clin Allergy* 1982; 12: 561–8.
10. OKUDA M. [Practice guideline for allergic rhinitis]. *Alerugi* 2002; 51: 541–3.
11. GAGA M, LAMBROU P, PAPAGEORGIOU N, et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000; 30: 663–9.
12. WRIGHT AL, HOLBERG CJ, MARTINEZ FD, HALONEN M, MORGAN W, TAUSSIG LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994; 94: 895–901.
13. LEYNAERT B, NEUKIRCH F, DEMOLY P, BOUSQUET J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000; 106: S201–5.
14. ASHER MI, WEILAND SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. *Clin Exp Allergy* 1998; 28 (Suppl. 5): 52–66; discussion 90–1.
15. PERONI DG, PIACENTINI GL, ALFONSI L, et al. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy* 2003; 33: 1349–54.
16. CORREN J. The connection between allergic rhinitis and bronchial asthma. *Curr Opin Pulm Med* 2007; 13: 13–8.
17. JOHNSTON SL, PATTEMORE PK, SANDERSON G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; 310: 1225–8.
18. PAPI A, JOHNSTON SL. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. *J Biol Chem* 1999; 274: 9707–20.
19. SIMONS E, SCHROTH MK, GERN JE. Analysis of tracheal secretions for rhinovirus during natural colds. *Pediatr Allergy Immunol* 2005; 16: 276–8.
20. DURHAM SR. Mechanisms of mucosal inflammation in the nose and lungs. *Clin Exp Allergy* 1998; 28 (Suppl. 2): 11–6.
21. BOUSQUET J, VAN CAUWENBERGE P, KHALTAEV N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: S147–334.
22. WATSON WT, BECKER AB, SIMONS FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993; 91: 97–101.
23. CORREN J, ADINOFF AD, BUCHMEIER AD, IRVIN CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992; 90: 250–6.
24. WOOD RA, EGGLESTON PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. *Am J Respir Crit Care Med* 1995; 151: 315–20.
25. MOLLER C, DREBORG S, FERDOUSI HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109: 251–6.
26. CRYSTAL-PETERS J, NESLUSAN C, CROWN WH, TORRES A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002; 109: 57–62.
27. CORREN J, MANNING BE, THOMPSON SF, HENNESSY S, STROM BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004; 113: 415–9.
28. MARTINEZ FD. Gene-environment interactions in asthma and allergies: a new paradigm to understand disease causation. *Immunol Allergy Clin North Am* 2005; 25: 709–21.
29. BIAGINI JM, LEMASTERS GK, RYAN PH, et al. Environmental risk factors of rhinitis in early infancy. *Pediatr Allergy Immunol* 2006; 17: 278–84.
30. OHSHIMA Y, YAMADA A, HIRAOKA M, et al. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. *Ann Allergy Asthma Immunol* 2002; 89: 265–70.