

Short communication

The prevalence of IgE sensitization to formaldehyde in asthmatic children

Background: Formaldehyde (FA) is well documented as a cause of occupational asthma. Recently, attention has been paid to FA as an allergen and a pollutant that enhances allergic sensitization. We have investigated the prevalence of FA-specific IgE in asthmatic children and the correlation between IgE sensitization to FA and the severity of asthma.

Methods: One hundred and fifty-five children were investigated, 122 of them asthmatic and 33 nonallergic. Specific IgE against FA was measured by CAP RAST. In addition, the patients answered a questionnaire, containing questions on clinical features of their asthma, their living conditions, and symptoms of mucosal irritation.

Results: Of all the subjects assessed, FA-specific IgE was detected in only two asthmatics, and their IgE levels of FA were low (0.42 and 0.46 UA/ml). One of the two patients with FA-specific IgE had severe asthma and frequent symptoms of mucosal irritation, but the other had mild asthma and only rare symptoms of mucosal irritation.

Conclusions: The prevalence of IgE sensitization to FA appears very low in Japanese children, whether or not they have asthma. Therefore, it appears likely that FA is not one of the major allergens causing childhood asthma.

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Recognition of numerous sources of formaldehyde (FA) in indoor environments has increased concerns about health hazards from this pollutant (1). Ambient FA, which primarily affects the upper airways and eyes as an irritant, has been shown to cause and exacerbate asthmatic symptoms (1–4); FA probably elicits airway inflammation associated with asthma, such as airway microvascular leakage, secretion into the airway lumen and denudation of airway epithelium (4, 5).

Intravenous FA has been shown to elicit systemic IgE-mediated anaphylaxis (6). Since inhaled FA is presumed to combine rapidly with a variety of proteins, such as albumin, there is a possibility that inhaled FA induces FA-specific IgE, and causes bronchoconstriction. However, no definite evidence for FA-specific IgE-dependent bronchospasm has been shown. Although FA appears to have little ability to produce IgE sensitization in adults (7–14), Wantke et al. (15) have reported elevated IgE levels to FA in 39% of 8-year-old children attending a primary school where indoor FA concentrations did not exceed 0.08 ppm. These studies suggest that children may be more susceptible to IgE sensitization to FA than are adults.

In recent years, the structure of houses in Japan has rapidly shifted to Western types and people now are living in very airtight rooms during most of their daily activities. Furthermore, in most houses, the ventilation systems for room air have been poor. These facts indicate that FA contamination in the room air of Japanese houses is a very serious problem, as several reports have warned (4, 16). In the present study, we have investigated the prevalence of FA-specific IgE in Japanese asthmatic children and the correlation between IgE sensitization to FA and severity of asthma.

Material and methods

Study groups

In July 1998, 122 asthmatic children (82 boys and 40 girls, mean age 9.5 years) and 33 nonallergic patients (21 boys and 12 girls, mean age 8.8 years) were randomly recruited from outpatient clinics in the department of pediatrics of our general hospitals. For this study patients were categorized as being asthmatic if they had ever been diagnosed as asthmatic by a pediatric allergologist, and if they also had clinical records of the current use of asthmatic drugs, or had experienced asthmatic attacks or episodic wheeze and shortness of

breath during the past year. On the other hand, patients who had no present or past history of asthma, allergic rhino-conjunctivitis, atopic dermatitis, or recurrent urticaria were chosen as nonallergic controls.

Assessment of formaldehyde-specific IgE and personal factors

Serum samples were obtained from all of the subjects, and kept frozen at -80°C until analysis. Levels of total serum IgE and FA-specific IgE were measured by Pharmacia CAP system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). A CAP level equal or greater than class 1 (0.35 UA/ml) was taken as positive.

Information on family history of physician-diagnosed asthma, characteristics of the dwelling, exposure to environmental tobacco smoke in the dwelling, and symptoms of mucosal irritation was collected from an interview questionnaire. The symptoms of mucosal irritation included irritation of the eyes, nose and throat, shortness of breath, and cough when they entered newly built houses, a poorly ventilated room, or stores dealing with clothing or furniture, in which FA concentration may be relatively high. Clinical features of asthma, included onset age, severity (mild, moderate, severe), immunologic factors (atopic/nonatopic), vulnerable season (seasonal/perennial), susceptible place (outdoor/indoor), and history of other allergic diseases. These features were usually determined by a pediatrician in charge of each subject, based on the clinical records. Classification of asthma severity was assessed in accordance with the *Guidelines for Diagnosis and Management of Childhood Asthma*, which was adopted by the Japanese Society of Pediatric Allergy and Clinical Immunology in 2000.

Statistical analysis

Statistical analyses on questionnaire data were performed as follows: chi-square test or Fisher's exact probability test was used when analyzing the relation between binary dependent and independent variables, and the Mann-Whitney *U*-test was applied to evaluate the significance of differences in age and total serum IgE between the two groups. A level of $P < 0.05$ was considered to be statistically significant.

This study was performed after written, informed consent was obtained from all of the children studied and their parents.

Results

Baseline characteristics of the asthmatic and nonallergic patients assessed in this study are shown in Table 1. The personal factors in terms of age, gender, family history of physician-diagnosed asthma, domestic exposure to tobacco smoke and symptoms of mucosal irritation, and characteristics of the dwelling were similar in the two groups. However, the median level of total IgE of asthmatics (755 IU/ml) was significantly higher than that of controls (108 IU/ml, $P < 0.01$). Among all the subjects, FA-specific IgE was detected by the Pharmacia CAP system in only two asthmatic children (Table 2); one exhibited 0.42 UA/ml of FA-specific IgE and the other 0.46 UA/ml. The former had severe asthma and frequent complaints of mucosal irritation in places where the FA

Table 1. Characteristics of subjects

	Asthmatic patients (<i>n</i> = 122)	Controls (<i>n</i> = 33)
Age (range, years)	9.5 (3–18)	8.8 (5–16)
Sex (M/F)	82/40	21/12
Severity of asthma		
Mild/moderate/severe	68/38/13 (3*)	–
Duration of asthma (range, years)	6.4 (0.5–16)	–
Immunologic factor		
Atopic/nonatopic	113/6 (3*)	–
Vulnerable season		
Perennial/seasonal	31/42/12 (37*)	–
Susceptible place		
Outdoor/indoor	2/90 (30*)	–
History of allergic diseases (%)		
Allergic rhino-conjunctivitis	69	–
Atopic dermatitis	47	–
Family history of asthma (%)		
Father/mother/siblings	11/14/43	9.4/18/33
Housing environment		
Detached/apartment	64/56 (2*)	20/13
Wood, mortar/steel, concrete	57/63 (2*)	19/14
Age of house		
0–5/5–10/>10 years	16/22/82 (2*)	7/7/19
Tobacco smoking indoors (%)	62	64
Symptoms of mucosal irritation		
Rarely/sometimes/often	90/22/8 (2*)	28/4/1

* Number of uncertain or unidentified answers.

level was likely to be high. On the other hand, the latter had mild asthma and rare complaints of mucosal irritation. There was no significant difference between the two groups in prevalence of IgE sensitization to FA.

For the asthmatic patients, we analyzed the relationship between mucosal irritability, assessed by the frequency (often/sometimes/rarely) of symptoms of mucosal irritation, and the clinical features of asthma and other personal factors that were described above. There was a significant relationship between severity of mucosal irritation and duration of asthma ($P < 0.05$), and between severity of mucosal irritation and tobacco smoking indoors ($P < 0.05$). No other significant relationships were observed. Because the prevalence of IgE sensitization to FA was very low in this study, it was impossible to evaluate the relationship between the existence of FA-specific IgE and the characteristics of asthma and mucosal irritation.

Discussion

We have shown that FA-specific IgE was detected in only two asthmatic children out of all the 155 subjects, including the nonallergic patients. Both patients with FA-specific IgE did not have severe asthma or frequent symptoms of mucosal irritation. These results suggest that the prevalence of IgE sensitization to FA may be

Table 2. Characteristics of two children with formaldehyde-specific IgE

	Patient 1	Patient 2
Age (years)	6	12
Sex	Male	Male
Formaldehyde-specific IgE (UA/ml)	0.42	0.46
Total serum IgE (IU/ml)	9800	1270
Severity of asthma	Severe	Mild
Onset of asthma (years)	2	6
Immunologic factor	Atopic	Atopic
Vulnerable season	Perennial	Seasonal
Susceptible place	Unsettled	Indoor
History of allergic diseases	AR, AD	AC, AD
Familial history of asthma	Father	—
Housing environment	Detached; wood, mortar	Detached; wood, mortar
Age of house (years)	>10	>10
Tobacco smoking indoors	No	No
Symptoms of mucosal irritation	Sometimes	Rarely

AR, allergic rhinitis; AC, allergic conjunctivitis; AD, atopic dermatitis.

rare in Japanese children and FA may not play an important role as an allergen causing asthma or as an irritant.

There is increasing evidence that exposure of adults to FA, even in relatively high concentrations, rarely evokes the production of specific IgE (7–14), and therefore FA-related asthmatic symptoms cannot be attributed to IgE sensitization to FA. This is consistent with our results on the allergenic properties of FA in asthmatic children. However, Wantke et al. (15) have found that the prevalence of IgE sensitization to FA is much higher in children than in adults. It is difficult to explain the reason for the discrepancy of prevalence of IgE sensitization in children; one possibility seems to be the difference in the method for measuring FA-specific IgE. Like Liden et al. (12) and Baba et al. (14), we measured it by a Pharmacia CAP system, because the system's specificity for measuring FA-specific IgE has been confirmed by RAST inhibition analysis using FA-human serum albumin conjugate as

an inhibitor (14). On the other hand, Wantke et al. (15) used Biomedica RAST (Freiburg, Germany) for their study of children. However, in another study, they measured FA-specific IgE by the same method in the 45 medical students, and showed that contrary to the children, the medical students had no significant levels of FA-specific IgE (13). Their results support the view that children may be more susceptible to IgE sensitization to FA than are adults. Taking into consideration our results, race differences might be another reason for the difference in IgE susceptibility to FA in children, although further development of precise methodology for detecting FA-specific IgE is necessary to resolve such inconsistencies.

A good correlation was found between severity of mucosal irritation and exposure to passive smoking in the home, which may be expected because tobacco smoke contributes to increased levels of indoor FA and volatile organic compounds (17), inducing mucosal irritation. Wantke et al. (15) have also shown a good correlation between FA concentrations in the classroom and symptoms likely caused by irritant action of gaseous FA, such as headache, rhinitis, cough, epistaxis, and fatigue. However, we have not measured FA concentrations in the subjects' residences. Therefore, it has not been confirmed that tobacco smoke leads to a serious contamination by FA. In our study, there was no significant difference between tobacco smoking in the home and the severity of asthma. In contrast, Smedje et al. (18) and Krzyzanowski et al. (19) have reported that asthma is more prevalent in children from indoor environments with higher FA levels.

In conclusion, FA-specific IgE may be found in a small proportion of children. However, as shown by Wantke et al. (15), there may be some population susceptible to FA behaving as an allergen, particularly in children. To date, indoor exposure to FA has not been proven as an important cause of immunologically mediated respiratory disease in adults. Our study also failed to reveal the clinical relevance of FA-specific IgE.

References

1. SAMET JM, MARBURY MC, SPENGLER JD. Health effects and sources of indoor air pollution. Part II. *Am Rev Respir Dis* 1988;**137**:221–242.
2. BARDANA EJ, MONTANARO A. Formaldehyde: an analysis of its respiratory, cutaneous, and immunologic effects. *Ann Allergy* 1991;**66**:441–452.
3. PAUSTENBACH D, ALARIE Y, KULLE T, et al. A recommended occupational exposure limit for formaldehyde based on irritation. *J Toxicol Environ Health* 1997;**50**:217–263.
4. SAKAMOTO T, DOI S, TORII S. Effects of formaldehyde, as an indoor pollutant, on the airway. *Allergol Int* 1999;**48**:151–160.
5. ITO K, SAKAMOTO T, HAYASHI Y, et al. Role of tachykinin and bradykinin receptors and mast cells in gaseous formaldehyde-induced airway microvascular leakage in rats. *Eur J Pharmacol* 1996;**307**:291–298.
6. MAURICE F, RIVORY J-P, LARSSON PH, JOHANSSON SGO, BOUSQUET J. Anaphylactic shock caused by formaldehyde in a patient undergoing long-term hemodialysis. *J Allergy Clin Immunol* 1986;**77**:594–597.
7. WILHELMSSON B, HOLMSTRÖM M. Positive formaldehyde-RAST after prolonged formaldehyde exposure by inhalation. *Lancet* 1987;**2**:164.

8. KRAMPS JA, PELTENBURG LTC, KERKLAAN PRM, SPIEKSMAS FTHM, VALENTIJM RM, DIJKMAN JH. Measurement of specific IgE antibodies in individuals exposed to formaldehyde. *Clin Exp Allergy* 1989;**19**:509–514.
9. GRAMMER LC, HARRIS KE, SHAUGHNESSY MA, et al. Clinical and immunologic evaluation of 37 workers exposed to gaseous formaldehyde. *J Allergy Clin Immunol* 1990;**86**:177–181.
10. DYKEWICZ MS, PATTERSON R, CUGELL DW, HARRIS KE, WU AF. Serum IgE and IgG to formaldehyde–human serum albumin: lack of relation to gaseous formaldehyde exposure and symptoms. *J Allergy Clin Immunol* 1991;**87**:48–57.
11. SALKIE ML. The prevalence of atopy and hypersensitivity to formaldehyde in pathologists. *Arch Pathol Lab Med* 1991;**115**:614–616.
12. LIDÉN S, SCHEYNIUS A, FISCHER T, JOHANSSON SGO, RUHNEK-FORSBECK M, STEJSKAL V. Absence of specific IgE antibodies in allergic contact sensitivity to formaldehyde. *Allergy* 1993;**48**:525–529.
13. WANTKE F, FOCKE M, HEMMER W, et al. Formaldehyde and phenol exposure during an anatomy dissection course: a possible source of IgE-mediated sensitization? *Allergy* 1996;**51**:837–841.
14. BABA K, YAGI T, NIWA S, et al. Measurement of formaldehyde-specific IgE antibodies in adult asthmatics. *Jpn J Allergol* 2000;**49**:404–411.
15. WANTKE F, DEMMER CM, TAPPLER P, GÖTZ M, JARISCH R. Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children. *Clin Exp Allergy* 1996;**26**:276–280.
16. KODAMA Y, MATUMURA T, KAWAMOTO T et al. Investigation for improving indoor air quality of domestic environments. In: Annual report of the pollution-related health damage compensation and prevention association of Japan. Tokyo: Nihon Kankyoeisei Center, 1993, pp. 233–293 (in Japanese).
17. HOULGATE PR, DHINGRA KS, NASH SJ, EVANS WH. Determination of formaldehyde and acetaldehyde in mainstream cigarette smoke by high-performance liquid chromatography. *Analyst* 1989;**114**:355–360.
18. SMEDJE G, NORBÄCK D, EDLING C. Asthma among secondary school children in relation to the school environment. *Clin Exp Allergy* 1997;**27**:1270–1278.
19. KRZYZANOWSKI M, QUACKENBOSS JJ, LEBOWITZ MD. Chronic respiratory effects of indoor formaldehyde exposure. *Environ Res* 1990;**52**:117–125.