

Original Article

Development of bronchial sensitization to inhalant allergens in occupational asthma patients

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ABSTRACT

In cases of occupational asthma due to reactive chemicals, an appreciable number of patients have persistent asthmatic symptoms and airway inflammation even after several years' avoidance of the cause agents. A case of late respiratory systemic syndrome (LRSS) caused by phthalic anhydride is reported. The patient showed a progression of bronchial asthma due to house dust mite and developed a new bronchial sensitization to horse hair during the 5 year follow-up period. The patient was diagnosed in September 1990 as having LRSS due to phthalic anhydride. He was atopic and had worked in a factory preparing materials for paints for 8 years. After leaving his workplace and commencing treatment with anti-asthmatic medications, his asthmatic symptoms and airway hyperresponsiveness were much improved for 1 year (PC20 methacholine level was increased from 0.44 to 4.4 mg/mL). For several months before the second admission (October 1992) his asthmatic symptoms were again aggravated and methacholine PC20 decreased to 1.1 mg/mL without improvement in the following 3 years. The level of serum specific IgE antibody to phthalic anhydride has been gradually decreasing, while specific IgE to two types of house dust mite and horse hair has been increasing year by year during the last 3 years' follow-up period. These findings suggest that chronic exposure to inhalant allergens can induce the progression of allergen-induced airway inflammation, and result in new bronchial sensitization to inhalant allergens. Careful follow-up study is needed

to detect new developments of allergen-induced bronchoconstriction in occupational asthma patients with persistent asthmatic symptoms.

Key words: allergen exposure, bronchial sensitization, house dust mite, occupational asthma.

INTRODUCTION

Phthalic anhydride (PA) is a common constituent of alkyd resins, which form the base for paints, varnishes and reinforced plastics. It is reported to be the most common agent in occupational asthma cases induced by acid anhydrides.^{1,2}

Further studies of acid anhydride (AA)-induced occupational asthma patients have revealed that most of them had a persistent airway hyperresponsiveness to methacholine and detectable levels of serum specific IgE antibodies to AA-human serum albumin conjugate after 6 years' avoidance of exposure.^{3,4}

Several studies have supported the relationship between house dust mite exposure, and sensitization to or increased risk of overt asthmatic symptoms.⁵ Sufficient amounts of house dust mite allergen to induce sensitization and provoke asthmatic symptoms have been detected in Korean houses.⁶ We report a case of late respiratory systemic syndrome (LRSS) where the patient showed sensitivity to house dust mite at first admission, and progressed to overt house dust mite-induced asthmatic symptoms after 4 years; in addition, the patient has newly developed horse hair-induced bronchoconstriction.

CLINICAL SUMMARY

The patient, a 38-year-old male was first admitted in September 1990. He had been employed for 8 years and 5 months prior to admission in a paint manufacturing

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factory. He began to feel shortness of breath, fever, headache, arthralgia and myalgia 8 months before admission. Allergy skin prick test revealed positive responses to *Dermatophagoides farinae* (2 SYMBOL 180\{ 'Symbol' 22<mm>), *Dermatophagoides pteronyssinus* (2 SYMBOL 180\{ 'Symbol' 20<mm>) and histamine (2 SYMBOL 180\{ 'Symbol' 2/33 SYMBOL 180\{ 'Symbol' 20<mm>), as well as to phthalic anhydride (8 SYMBOL 180\{ 'Symbol' 4/33 SYMBOL 180\{ 'Symbol' 27<mm>). Total IgE level by paper radio-immunosorbent test (PRIST) was 72 IU/mL and radio-allergosorbent test (RAST) to *D. farinae* and *D. pteronyssinus* yielded negative results. Chest radiograph showed no abnormal finding before or after PA challenges. Methacholine PC20 level was 0.44 mg/mL. The *D. farinae* bronchoprovocation test showed a negative result as shown in Fig. 1a. The patient's sensitivity to PA was confirmed by PA-bronchoprovocation test as described previously.⁷

CLINICAL COURSE

Subsequent to diagnosis in October 1990, the patient left his workplace, and took anti-asthmatic medications including a bronchodilator and inhaled corticosteroid. The patient had never been exposed to horse hair and had no history of high exposure to house dust mite allergen. His airway hyperresponsiveness improved to 4.4 mg/mL after 1 year (September 1991) with improvement of his clinical symptoms. In the second year, he began to complain of aggravation of the asthmatic symptoms, and his airway hyperresponsiveness ceased to improve. When a second allergy skin prick test was done after 4 years (September 1994), skin reactivity and specific IgE antibody level to *D. farinae* and *D. pteronyssinus* were much

increased as shown in Table 1. Bronchoprovocation test with *D. pteronyssinus* showed an early asthmatic response as shown in Fig. 1b. After 5 years (September 1995), skin reactivity and specific IgE level measured by a Diagnostic Products Corporation system (Los Angeles, CA, USA) to *D. farinae* and *D. pteronyssinus* was further increased compared to the 1994 results. Skin positive responses to horse hair were noted first in September 1995. A comparison of specific IgE levels to inhalant and to occupational allergens over the 5 years showed a progressively increasing pattern of reaction to horse hair and house dust mites, with a progressive decline in specific IgE antibodies to PA and trimellitic anhydride (Table 1).

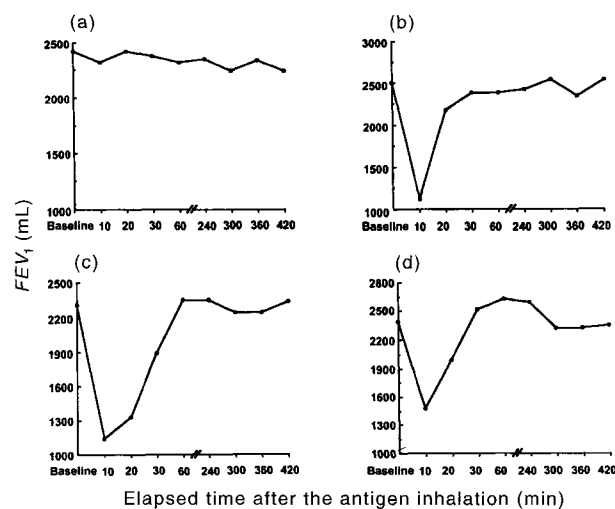


Fig. 1 (a) Bronchoprovocation test (BPT) with *Dermatophagoides farinae* at the first admission (1990) showing a negative result. (b) BPT with *D. pteronyssinus* after 4 years (1994). (c) Repeat BPT with *D. farinae* in 1995. An early asthmatic response was noted. (d) BPT with horse hair after 5 years (1995). An early asthmatic response was noted.

Table 1. Changes of specific IgE antibodies and airway hyperresponsiveness in the study patient

	Follow-up duration (months)						
	0	1	6	12	24	48	60
Total IgE level (IU/mL)	67	103	118	79	272	114	114
Dpt-specific IgE	0.5	0.7	0.9	0.9	3.4	3.6	8.9
Dfa-specific IgE	0.2	0.9	0.2	1.7	2.0	2.2	3.0
HH-specific IgE	0.3	0.6	1.8	1.7	1.2	3.9	5.2
PA-specific IgE	47.3	58.5	87.2	54.3	34.9	19.2	15.1
TMA-specific IgE	14.9	18.6	19.3	14.2	6.4	2.6	1.7
Methacholine PC20 (mg/mL)	0.44		2.5	4.4	1.25	2.53	2.5

PA, phthalic anhydride; TMA, trimellitic anhydride; HH, horse hair; Dpt, *D. pteronyssinus*; Dfa, *D. farinae*; BPT, bronchoprovocation test.

Specific IgE to the latter disappeared after 4 years' avoidance, while specific IgE to PA fell year by year, but was still detected in his serum. A bronchoprovocation test with horse hair showed an early asthmatic reaction (Fig. 1d). His airway hyperresponsiveness to methacholine showed a maximum improvement in the first 12 months of avoidance, which abated in the following years and stabilized at 2.5 mg/mL.

DISCUSSION

The acid anhydrides such as phthalic and trimellitic constitute a group of low-molecular-weight chemicals against which a specific antibody has been reliably and repeatedly demonstrated.^{4,8,9} A follow-up study of tetrachlorophthalic anhydride (TCPA) asthma after 4 years of avoidance suggested that specific IgE fell exponentially with a half-life of 1 year but it was still detected in serum when there was persistent bronchial hyperresponsiveness.⁴ In our study, the patient had complained of persistent asthmatic symptoms with persistent airway hyperresponsiveness, and specific IgE antibody to PA was still detected in his serum after 5 years' avoidance.

Venable *et al.* suggested that persistence of serum and skin responses to TCPA indicated continuing antibody production after avoidance of exposure.⁴ The half-life of 1 year contrasts with the half-life of intravenous radio-labeled IgE myeloma protein of only 2.5 days in normal subjects and 5.1 days in a patient with IgE myeloma.¹⁰ This difference could not be explained by continuing TCPA exposure, as all the patients had left the factory. It is conceivable that TCPA exposure can continue if it is retained in the lungs, either bound to particles of epoxy resin powder or to tissue proteins, or if it is absorbed from the lungs and retained in extrapulmonary tissue, but the possibility of such retention has not been studied *in vivo*. Autonomous IgE production, unrelated to allergen exposure, has been suggested as an explanation for the slow decline in anti-ragweed IgE antibody.¹¹ Long-lived, radio-resistant B cells have been described in animals, which continue to produce IgE in the absence of allergen exposure.¹² In the present study, specific IgE antibody to PA fell for 5 years, but was still detected in spite of cessation of exposure. Further investigations are needed to discover how these specific IgE antibodies persist after several years' avoidance.

Chronic antigenic challenge might induce the histologic characteristics of airway inflammation that caused

persistent airway hyperresponsiveness in a non-allergic rat.¹³ House dust mite is the most common inhalant allergen in Korea. Sufficient amounts of the group I allergen in *D. farinae* and *D. pteronyssinus* to induce sensitization and/or to aggravate asthmatic symptoms have been detected in the environment of Korean houses.⁶ The patient in the present study was weakly sensitized to house dust mite at his first admission, although the bronchoprovocation test and RAST to *D. farinae* showed a negative result. Specific IgE antibody gradually increased with chronic house dust mite exposure, which induced progression of airway inflammation and was confirmed by the house dust mite-bronchoprovocation test. With respect to horse hair, there was no evidence of sensitization at first admission or during the 4 years following. The patient had no history of intensive exposure to horse hair, but sensitization to horse hair was noted 5 years after first admission, and the specific IgE antibody level progressively increased, until inhalation of horse hair extracts provoked bronchoconstriction in 1995. High levels of eosinophils, mast cells, and lymphocytes have been found in the airway mucosa accompanied by disruption of epithelial cells in both allergic and isocyanate-induced asthma.¹⁴⁻¹⁶ Toluene 2,4-diisocyanate (TDI) exposure also involved structural epithelial changes but only a marginal increase in the absorption of luminal molecules, and TDI-asthma rhinitis was associated with plasma exudation and hyperresponsiveness.¹⁷ These findings suggest that exposure to an inhalant allergen can induce new sensitization and/or aggravate allergen-induced airway bronchoconstriction. Loss of the airway mucosa barrier in occupational asthma patients with continuing airway hyperresponsiveness might make them more susceptible to IgE-sensitization to an inhalant allergen, possibly by decreasing the barrier to absorption.

Cross-allergic responses to structurally allied anhydride chemicals has been reported.¹ Such IgE antibody responses to hapten or new antigenic determinant from reactive chemicals were demonstrated to be heterogeneous.^{18,19} In the present study, specific IgE binding to TMA might be caused by cross-allergenicity between PA and TMA. These findings suggest that chronic exposure to an inhalant allergen can induce progression and/or induce allergen-induced airway inflammation in occupational asthma patients with remaining airway inflammation. Careful regular examinations, including allergy skin test and RAST, should be conducted to detect new sensitization to inhalant allergens during the follow-up period.

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