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Effects of cigarette smoking on IgE-mediated allergy in elderly patients with asthma

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Abstract : The influence of cigarette smoking on the pathophysiology of asthma in the elderly remains controversial. In this study, the inluence of cigarette smoking on IgE-mediated allergy including the generation of leukotrienes B4 (LTB4) and C4 (LTC4) was examined in forty asthmatics over the age of 70 years (20 ex-smokers and 20 never-smokers), and 20 patients with pulmonary emphysema over age 70 (all ex-smokers). The frequency of patients with serum IgE more than 200 IU/ml was significantly larger in smoking asthmatics than in non-smoking asthmatics. The incidence of patients with positive RAST score for inhalant allergens, was also significantly higher in patients with a history of smoking than in those without a smoking history. There were no significant differences in the frequency of patients with positive RAST and those with serum IgE more than 200 IU/ml between non-smoking asthmatics and patients with pulmonary emphysema. The generation of leukotriene B4 (LTB4) by leukocytes was significantly more increased in ex-smokers than in never-smokers in the elderly asthmatics. The results suggest the possibility that cigarette smoking enhances IgE-mediated allergy in elderly patients with asthma.

Key words : cigarette smoking, IgE-mediated allergy, LTB4, LTC4 generation, elderly asthmatics

Introduction

The chronic sidestream cigarette smoke (SS) exposure has been reported to enhance the existing symptoms of allergic airway disease. However, the following question "does cigarette smoke exposure lead to the induction of asthma in a nonsusceptible individual?" is an important problem. SS in combination with allergen does not induce an allergic airway response in nonsusceptible animals. Several studies show SS exposure is associatiated with the induction or exacerbation of asthma[1-3]. Cigarette smoke may act as a sensitivity trigger so that other potential triggers such as viral infection may have a

greater impact in the induction of asthma[4].

Several studies for infants at the age from 6 to 10 years found that exposure to cigarette smoke is not associated with the development of asthma[5,6]. Atopic status to inhaled allergens, which is closely related to the development of childhood asthma, is not clearly associated with cigarette smoke exposure[7]. Exposure to cigarette smoke increases sensitization to food allergens in the few years of life[8], but not associated with sensitization to inhaled allergens[9].

In the present study, the influence of cigarette smoke on IgE-mediated allergy including the generation of leukotrienes B4 (LTB4) and C4 (LTC4) by leukocytes was examined in elderly asthmatics with a history of smoking more than 20 years.

Subjects and Methods

The influence of cigarette smoke on IgE-mediated allergy was examined in 20 asthmatics who had a history of smoking for more than 20 years (50.1 pack-year). The other 20 asthmatics were never-smokers. All forty asthmatic subjects over the age of 70 years (14 women and 26 men), and 20 subjects with pulmonary emphysema (mean age 75.3 years, all men and all smokers) were recruited from Misasa Medical Center. The mean age of elderly asthmatics was 74.9 years and age at onset of the disease was 59.2 years.

Asthma was diagnosed according to the definition proposed by the American Thoracic Society[10]. The asthmatic subjects were stable with no changes in asthma symptoms and medication for at least 1 month, except for the use of short acting β_2 agonists.

Spirometry was performed by means of a CHESTAC 33 (Chest Co, Tokyo, Japan) linked to a computer when their symptoms were stable. The following measurements were performed on all subjects : forced vital capacity (FVC), FEV_1, and FEV_1/FVC.

Serum IgE was measured by radioimmunosorbent test (RIST), and IgE antibodies specific to aeroallergenns including house dust mite, pollens, moulds, and animal danders were measured using the Pharmacia CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden).

The amounts of LTC4 and LTB4 generated by the peripheral leukocytes were assessed as previously described[11-13]. Five milliliters 6% dextran (molecular weight ~200,000 kDa (Nacalai Teque, Inc., Kyoto, Japan) were added to 20 mL of heparinized peripheral blood, and the mixture was left for 1 hour at room temperature. The leukocytes-rich plasma supernatant was then removed and used. The number of cells was adjusted to $5x10^6$ cells/mL in Tris CM, and 1 mcg of calcium ionophore A23187 (Sigma, St Louis, Mo, USA) was then added to the cell suspension. The solution was mixed and incubated for 15 minutes at 37℃. After a 4x volume of prechilled ethanol (final, 80%ethanol) was added. This was centrifuged at 3000 rpm for 30 minutes. The filtrate through a syringe filter (Toyo Roshi Co, Tokyo, Japan) was decompressed and dried to solid. LTC4 and LTB4 were quantified by means of high-performance liquid chromatography. As described by Lam et al[14]. Quantities of LTC4 and LTB4 were expressed as nanograms per $5x10^6$ cells.

Statistically significant differences of the mean were estimated using the unpaired Student't test and β_2 test. A p value of <0.05 was regarded as significant.

Results

The mean level of serum IgE was the highest in elderly asthmatics with a history of smoking

(527 IU/ml) compared with the levels in asthmatics without smoking history (451 IU/ml) and patients with pulmonary emphysema (355 IU/ml). However , significant differences were not found in the mean of serum IgE among the three study groups. In contrast, the incidence of subjects with serum IgE levels over 200 IU/ml was higher in ever-smokers of elderly asthmatics (80.0%) compared with never-smokers of elderly subjects (40.0%) and subjects with pulmonary emphysema (20.0%), and the difference was significant between ever-smokers and never-smokers of elderly asthmatics ($p<0.05$) (Fig. 1).

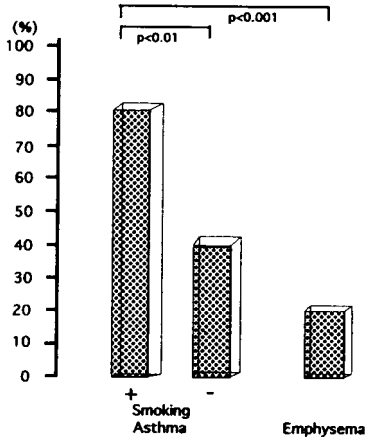

Fig.1. Frequency of patients with serum IgE more than 200 IU/ml in asthma and pulmonary emphysema in relation to cigarette smoke

The incidence of subjects with a positive RAST score against inhalant allergens was more significantly increased in ever-smokers than in never-smokers of asthmatics ($p<0.02$). The difference between never-smokers of elderly asthmatics and patients with pulmonary emphysema was also significant ($p<0.001$), however, no significant difference was found between never-smoker of asthmatics and those with pulmonary emphysema, as shown in Fig. 2.

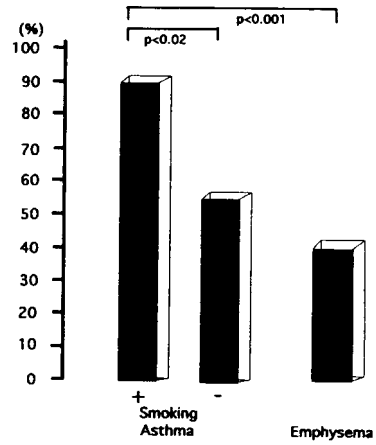

Fig.2. Frequency of patients with positive RAST score for inhalant allergens in asthma and pulmonary emphysema in relation to cigarette smoke

The generation of LTC4 by leukocytes was not significantly different among asthmatics with or without smoking history, and patients with pulmonary emphysema. Regarding LTB4 generation, a significant difference was observed between ever-smokers and never-smokers of the elderly asthmatics ($p<0.001$). The LTB4 generation was also significantly more increased in subjects with pulmo-nary emphysema compared with never-smokers of elderly asthmatics ($p<0.01$), as shown in Fig. 3.

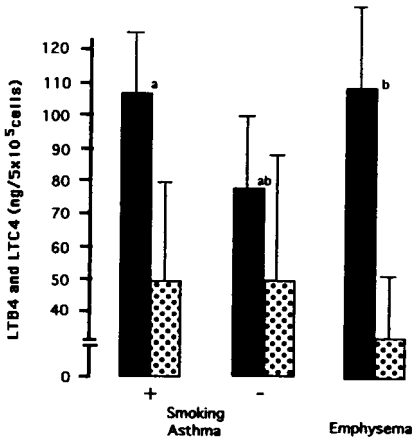

Fig.3. Generation of leukotriene B4 (LTB4) (■) and C4 (LTC4) (▨) by leukocytes in patients with asthma and pulmonary emphysem. a;p<0.001, b;p<0.01.

Discussion

The relationship between smoking and allergy has been reported to be complex[15]. During the first 3 years of life, both prenatal and postnatal exposure to ETS appears to have an adjuvant effect on allergic sensitization[9,16,17]. Exposure to cigarette smoke increases sensitization to food allergens in a few years of life[8], but not associated with sensitization to inhaled allergens[8,9]. Smoking is known to increase the inflammatory burden of the lower respiratory tract through a number of related but separate mechanisms. These include the recruitment of increased numbers of inflammatory cells, alteration in cell subtype, enhancement of some cellular functions, and proinflammatory mediator release[18].

In this study, a relationship between cigarette smoke and IgE-mediated allergy was examined in elderly asthmatics with a long-term history (more than 20 years) of smoking. The frequency of subjects with serum IgE more than 200 IU /ml, and the incidence of subjects having IgE antibodies specific to inhalant allergens were significantly higher in ever-smokers than in never-smokers of the elderly asthmatics. This might suggest that long-term cigarette smoking enhances IgE-mediated allergy. Furthermore, the generation of LTB4 by leukocytes was significantly more increased in ever-smokers than in never-smokers of asthmatics. Our previous studies have shown that the presence of specific IgE antibodies against inhalant allergens enhances LTC4 generation, bronchial hyperresponsiveness and the relationship between LTC4 and airway obstruction[12], and further that increased generation of LTB4 is closely related to bronchial hyperresponsiveness in patients with asthma[12]. These results may suggest that cigarette smoke influences IgE-related allergy including production of IgE antibodies, and generation of LTs in elderly patients with asthma.

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高齢者喘息のIgE にmediateされるアレルギー反応におよぼす喫煙の影響

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高齢者喘息の病態に対する喫煙の影響については，なお不明な点が多い。本研究では，70歳以上の気管支喘息40例（喫煙歴20年以上の症例20例，非喫煙症例20例）および70歳以上の肺気腫20例（全例喫煙者）を対象に，IgE-mediated allergy（LTB4，LTC4の産生を含む）に対する喫煙の影響について検討した。血清IgE値が200IU／ml以上を示す症例の頻度は，喘息の喫煙例で非喫煙例や肺気腫症例と比べ有意に高い値を示した。吸入抗原に対する特異的IgE抗体が陽性を示す症例の頻度は，喘息の喫煙例で非喫煙例や肺気腫に比べ有意に高い値を示した。しかし，血清IgEが200 IU／ml 以上の症例の頻度およびRAST陽性例の頻度は，喘息の非喫煙例と肺気腫例の間には有意の差は見られなかった。LTB4 の産生は，喘息の喫煙例で，非喫煙例と比べ有意の亢進が見られた。また，肺気腫例では，喘息の非喫煙例に比べ，有意に高い産生が見られた。しかし，LTC4の産生には喘息の喫煙例，非喫煙例，肺気腫例の間に有意の差は見られなかった。