◎原 著

Effects of aging on the pathophysiology of asthma observed by IgE-mediated allergy, pulmoanry function, low attenuation area of the lungs on HRCT, and LTB4, LTC4 generation

Fumihiro Mitsunobu, Kozo Ashida, Yasuhiro Hosaki[1], Hirofumi Tsugeno, Norikazu Nishida, Takuya Nagata, Tadashi Yokoi[1], Shingo Takata and Yoshiro Tanizaki

Division of Medicine, [1]Division of rehabilitation, Misasa Medical Center, Okayama University Medical School.

Abstract : The influence of aging on the pathophysiology of asthma in the elderly was examined in 40 patients (20 younger asthmatics under the age of 50 years, mean age 32.5 years and 20 elderly asthmatics over the age of 70 years, mean age 74.3 years), relating to IgE-mediated allergy, pulmonary function, low attenuation area (LAA) of the lungs on HRCT, and the generation of leukotrienes B4 (LTB4) and C4 (LTC4) by leukocytes. The frequency of patients with serum IgE of more than 200 IU/ml, and the incidence of those with a positive RAST score for inhalant allergens were significantly higher in younger patients than in elderly subjects. The values of %FVC, %FEV_1 and FEV_1% were significantly larger in younger patients compared with elderly subjects. The %RV was significantly larger in elderly patients than in younger patients, however, the difference in %DLco was not significant between the two age groups. The LAA of the lungs on HRCT and the ratio of expiratory LAA (exp LAA) to inspiratory LAA (ins LAA) were also significantly larger in elderly asthmatics than in younger sub-jects. The generation of LTB4 and LTC4 was larger in younger patients than in elderly subjects, and LTB4 generation was significantly larger in younger subjects compared with elderly subjects. These results suggest that changes in IgE-mediated allergy, airflow and lung volume accompanied with hyperinflation are often observed in elderly asthmatics.

Key words : IgE-mediated allergy, pulmonary function, elderly asthmatics, HRCT, %RV

Introduction

IgE-mediated allergy is well known to participate in the onset mechanisms of asthma. The IgE-mediated allergic reaction has been shown to change qualitatively and quantitatively with aging[1-5]. Previous studies have shown that bronchial reactivity to methacholine and histamine release from leukocytes show a tendency to decrease with aging[6].

There are two different views regarding the significance of IgE antibodies in the pathogenesis of asthma. One is that asthma is clinically classified into two types, atopic and non-atopic, on the basis of the presence or absence of IgE-mediated reactions[7], where atopic asthma is more often found in the younger population and non-atopic asthma is found in the older patients. In contrast, there is a second concept that asthma is almost always associated with some type of igE-related reaction[8,9].

Our previous studies have suggested that the frequency of patients with a family history of asthma was relatively high, even in patients between the ages of 50 and 59 years at onset (mean patient age 63.4 years ; 61.1%) and in those over the age of 60 years at onset (mean patient age 74.0 years ; 37.9%)[10]. These results reveal that many elderly asthmatics have an allergic constitution.

In the present study, the influence of aging on the pathophysiology of elderly asthmatics was examined in relation to IgE-mediated allergy, pulmonary function, low attenuation area (LAA) of the lungs on HRCT, and the generation of LTC4 and LTB4 by leukocytes.

Subjects and Methods

The subjects were 20 asthmatics over the age of 70 years (14 women and 6 men), and 20 asthmatics under the age of 50 years (13 women and 7 men, mean age 32.5 years). The mean age of elderly subjects was 74.3 years and age at onset of the disease was 53.6 years. All subjects were never-smokers. Asthma was diagnosed according to the definition proposed by the American Thoracic Society[11], as previously described[12]. 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.

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

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 (FEV_1%). Residual volume (RV) was measured by body plethysmography (Autobox 2800, Chest Co, Tokyo, Japan). The diffusing capacity for carbon monoxide (DLco) was measured by the single breath technique using a CHESTAC 33. The actual DLco values were corrected for hemoglobin and carbon monoxide levels. The FVC, FEV_1, RV, and DLco measurments for each patient were expressed as a percent of the predicted values.

All subjects had a modified HRCT scan of the lungs with a Toshiba Xpeed scanner (Toshiba, Tokyo, Japan) using the thin section (2 mm collimation) technique and a high-resolution

reconstruction algorithm. An intravenous contrast medium was not administered. The scanning time was 2.7 seconds, tube current was 200 mA, and voltage was 120 kVp. Maximal inspiratory and maximal expiratory HRCT scans were obtained at the following three selected anatomic levels as described by Miniati et al. [13] : (1) top of the aortic arch, (2) origin of the lower lobe bronchus, and (3) 3 cm above the top of the diaphragm. The relative area of the lungs with an attenuation value lower than -950 HU (LAA) from the three anatomic lung levels was obtained both at full inspiration inspiratory RA_{950} and full expiration expiratory RA_{950}. The %LAA value was expressed as the mean of inspiratory RA_{950} at three anatomic lung levels. The ratio of expiratory RA_{950} to inspiratory RA_{950} (exp LAA/ins LAA) was also calculated.

The amounts of LTC4 and LTB4 generated by the peripheral leukocytes were assessed as previously described[14-16]. Five milliliters 6% dextran (molecular weight -200,000 kDa (Nacalai Tequ e, 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 C. 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[17]. Quantities of LTC4 and LTB4 were expressed as nanograms per $5x10^6$ cells.

Informed consent was obtained from all subjects and the study protocol was approved by the ethics committee of our institution.

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

Results

The mean serum IgE level was higher in young asthmatics than in elderly asthmatics, however, the difference was not significant.

The frequency of patients with serum IgE level of more than 200 IU/ml was significantly larger in young subjects than in elderly subjects ($p<0.05$). The incidence of subjects with a positive RAST score for inhalant allergens was significantly higher in younger asthmatics compared with elderly asthmatics ($p<0.02$) (Table 1).

Table 1. Serum total IgE levels and frequency of patients with a positive RAST score against inhalant allergens in young and elderly patients with asthma

Subjects	Serum IgE (IU/ml)	No of patients with 200 IU/ml<S-IgE	2+<RAST score*
Young asthma	1242 (86-5195)	15/20(75.0%) [a]	18/20(90.0%) [b]
Elderly asthma	417 (11-2918)	8/20(40.0%) [a]	11/20(55.0%) [b]

*No of patients with a positive RAST score against inhalant allergens. a;p<0.05, d;p<0.02.

The values of %FVC (108.3±14.6%), $\%FEV_1$ (83.2±16.5%) and $FEV_1\%$ (FEV_1/FVC) (73.7±12.9%) in young asthmatics were significantly larger compared with %FVC (83.7±16.1%, $p<0.001$), $\%FEV_1$ (73.2±20.3%, $p<0.01$), and $FEV_1\%$ (63.5±9.3%, $p<0.001$) in elderly asthmatics (Fig. 1). The %RV value was significantly larger in elderly asthmatics (129.1±25.4%) than in younger asthmatics (106.9 21.2%0) ($p<0.01$) (Fig. 2).

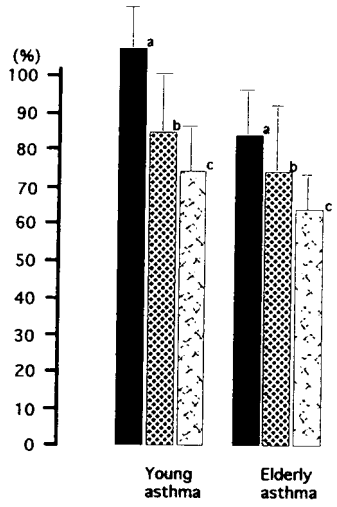

Fig.1. Comparison in %FVC (■), %FEV1 (▨) and FEV1 % (▨) values between young and elderly patients with asthma. a and c; p<0.001, b;p<0.01.

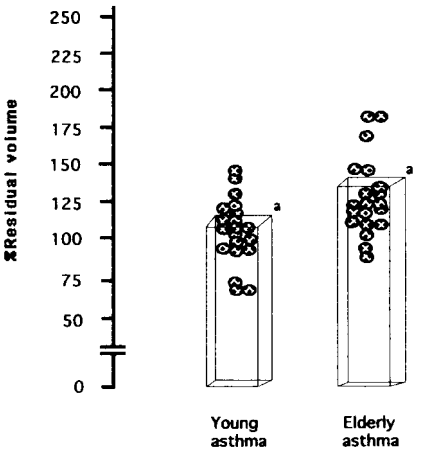

Fig.2. Comparuison in %Residual volume (RV) between young and elderly patients with asthma. a:p<0.01.

The %DLco valuue was higher in young subjects with asthma (97.7±12.1%) than in elderly asthmatics (90.6±16.7%). However, there was no significant difference in %DLco value between young and elderly asthmatics (Fig. 3)

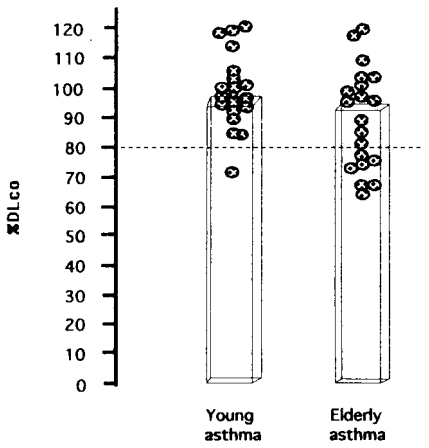

Fig. 3. Comparison in %DLco between young and elderly patients with asthma

The %LAA <-950 HU (RA_{950}) of the lungs on HRCT was significantly larger in elderly asthmatics (10.9±7.4%) compared with young subjects with asthma (6.1±5.6%) (p<0.05) (Fig. 4).

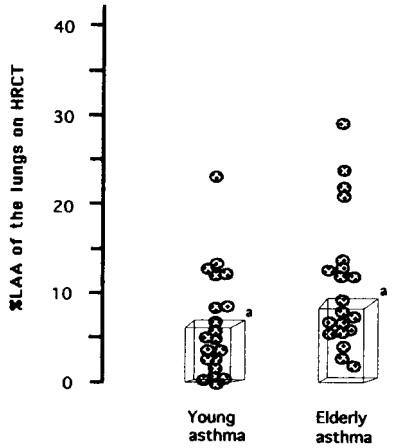

Fig.4. %LAA of the lungs on HRCT in patients with asthma. a:p<0.05.

The exp LAA/ins LAA was also significantly higher in elderly asthmatics (0.17±0.11) compared with young subjects with asthma (0.04±0.04) (p<0.001) (Fig. 5).

The generation of LTC4 by leukocytes was more increased in young subjects with asthma (61.5±27.0 ng/5x10^6 cells) compared to

elderly asthmatics (49.3±39.0 ng/5x10^6 cells). However, there was no significant difference in LTC4 generation between young and elderly as thmatics. The LTB4 generation was significantly more increased in young subjects with asthma (110.4±37.6 ng/5x10^6 cells) than in elderly asthmatics (77.1±22.4 ng/5x10^6 cells) ($p<0.01$) (Fig.6).

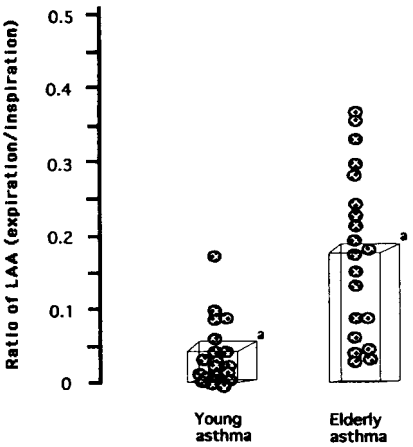

Fig.5. Ratio of expiratory LAA / inspiratory LAA in elderly patients with asthma. a:p<0.001.

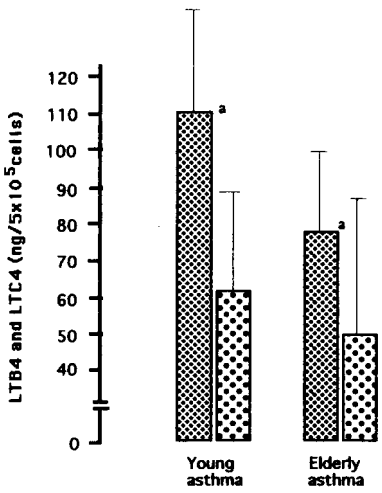

Fig.6. Generation of leukotriene B4 (LTB4) (▨) and C4 (LTC4) (□) by leukocytes in patients with asthma. a;p<0.01.

Discussion

It is well known that the pathophysiology of asthma, including IgE-mediated allergy, pulmonary function, and emphysematous changes of the lungs, change with aging. In IgE-mediated allergy, the release of chemical mediators such as histamine and leukotrienes, occurs in the early stage of an asthma attack and inflammatory cell infiltration occurs in the airways at the late stage. In the inflammatory process, lymphocytes[18], neutrophils[19], eosinophils[20] and basophils[21] have been observed by analyzing the cellular composition of bronchoalveolar lavage (BAL) fluid. IgE-mediated allergic reactions are affected by aging[3]. In this study, the frequency of patients with a serum IgE level of more than 200 IU/ml, and the incidence of those with a positive RAST score (2+<) were significantly higher in younger asthmatics than in elderly asthmatics.

The results show that IgE-mediated allergy showed a tendency to decrease in elderly patients with asthma over the age of 70 years.

Regarding pulmonary function, the values of %FVC, %FEV_1, FEV_1%, and %RV were significantly more decreased in elderly patients over age 70 compared with the values in younger subjects.

The value of %DLco was also more decreased in elderly asthmatics over age 70 than in younger asthmatics, however, this difference was not significantl.

The relative area of the lungs with attenuation values less than -950 HU (RA_{950}) on HRCT scans obtained at full inspiration is found to be an objective measure of the extent of pulmonary emphysema by comparison with histopathologic data[22,23]. Our previous studies demonstrated that RA_{950} correlated with parameters of airflow limitation

(%FFV_1, FEV_1/FVC, %FEF_{25-75}) and lung volume (%TLC, %FRC, %RV), but not with lung transfer factor (%T_{LCO}, %T_{LCO}/VA)[12]. Previous studies showed that the RA_{950} of the lungs on HRCT was significantly larger in asthmatics with a smoking history compared with those without a smoking history[24]. The RA_{950} is also influenced by aging and disease severity in asthmatics without a smoking history[12]. In this study, the mean RA_{950} and the ratio of expiratory LAA to inspiratory LAA were significantly larger in elderly asthmatics than in young subjects with ast hma. The ratio could be divided into two degrees as follows : <0.5 and $0.5<$. The ratio more than 0.5 was shown only in asthmatics with a history of smoking and subjects with pulmonary emphysema. All the subjects in this study showed the ration less than 0.5, because they were all non-smokers. The results suggest that the LAA_{950} in asthma is influenced by aging. However, the influence by aging is not sostrong as cigarette smoking in relation to RA_{950}.

The generation of LTB4 and LTC4 by leukocytes was also affected by aging. The amount of LTB4 and LTC4 generation was more increased in younger asthmatics than in elderly asthmatics over age 70. The amount of LTB4 generation by leukocytes was significantly larger in younger asthmatics compared with elderly patients with asthma, however, the difference in LTC4 generation was not significant between younger and elderly asthmatics. These results reveal that changes in IgE-mediated allergy, pulmonary function, %LAA of the lungs on HRCT, and LTB4, LTC4 generation by lerukocytes are found in elderly asthmatics over age 70, compared with younger subjects with asthma.

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IgEにmediatedされるアレルギ反応ー，肺機能，HRCT上の肺のlow attenuation area (LAA)，および LTB4，LTC4産生から見た喘息の病態に対する加齢の影響

光延文裕，芦田耕三，保﨑泰弘[1)]，柘野浩史，西田典数，永田拓也，横井　正[1)]，高田真吾，谷崎勝朗

岡山大学医学部附属病院三朝医療センター内科，[1)]リハビリテーション科

70歳以上の気管支喘息20例(平均年令74.3歳)および50歳以下の気管支喘息20例（32.5歳）を対象に，IgEにmediateされるアレルギー反応，肺機能，HRCT上の肺のLAAの程度，白血球によるLTB4，LTC4産生などに対する加齢の影響について検討した。血清IgE値が200 IU／ml以上の症例の頻度および吸入抗原に対するRAST scoreが陽性を示す症例の頻度は，いずれも若青年者喘息で高齢者喘息と比べ有意に高い傾向を示した。%FVC，%FEV_1，FEV_1%値はいずれも若青年者喘息で高齢者喘息に比べ有意に高い値を示し，また，%RVは高齢者で有意に高い値が示された。一方，%DL_{CO}は両者間に有意の差は見られなかった。HRCT上の%LAAおよびLAA比（呼気／吸気）いずれも高齢者喘息で有意に高い値を示し，加齢により肺のLAAが明らかに影響を受けることが判明した。LTC4の産生は若青年者喘息でやや高い値が示されたが，高齢者との間に有意差は見られなかった。一方，LTB4産生は，若青年者喘息で高齢者喘息と比べ有意に高い値が示された。これらの結果は，70歳以上の高齢者喘息では加齢による影響を広範囲にわたり受けている可能性が高いことを示している。