
◎原 著

Humoral and cellular immune response in elderly patients with bronchial asthma

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Abstract : Humoral and cellular immune responses in bronchial asthma were examined by comparing the results of older asthmatics (group OA) with those of older healthy subjects (group OH) and of younger asthmatics (group YA). In humoral immune response, IgE-mediated immune system expressed by elevated serum IgE levels and IgE antibodies for house dust mite (HDm) and/or *Candida albicans* was clearly found in older asthmatics, while there was no finding showing the presence of IgE-mediated immune response in older healthy subjects. There was no significant difference in levels of serum IgG and IgA among the three groups. However, the serum IgM level was significantly lower in older asthmatics than in younger asthmatics. IgE antibodies to HDm and/or *Candida albicans* were more frequently found in older asthmatics compared with older healthy subjects. In contrast, IgG₄ antibodies to HDm were not different among the three groups. IgG₄ antibodies to *Candida albicans* were significantly higher in both older groups than in younger group. However, there was no significant difference between asthmatic and healthy subjects in the elderly. Delayed skin reaction to PPD was significantly more decreased in older asthmatics. These results show that bronchial asthma in the elderly is characterized by the presence of IgE-mediated immune response and by the changes of immune response with aging.

Key words : IgE, IgG₄, Immunoglobulins, PPD, Bronchial asthma

Introduction

Among the various immunoglobulins,

immunoglobulin E (IgE) is identified as the antibody causing immediate type of immune response (1, 2), which plays the major role

in atopic or extrinsic types of asthma (3–5). These types of asthma are considered to be the predominant form of the disease in children and young adults. In contrast, nonatopic or intrinsic asthma seems to be more popular among older patients. Regarding IgG antibodies, increased levels of IgG₄ antibodies have been shown in patients with immunotherapy with offending allergen (6–9), and in those with food allergy (10, 11). The role of IgG₄ antibodies are, however, still unclear in immediate immune response. In addition to these humoral immune responses, depressed cell-mediated immune response related to IgE-mediated immune reaction has been shown (12–14). The role of cell-mediated immunity in bronchial asthma is not known.

Bronchial asthma of elderly subjects is characterized by qualitative and quantitative changes of immune response (15, 16), and by pathophysiological changes in the airways (17). Despite an increased number of elderly patients with bronchial asthma in recent years, there are few reports about characteristics of humoral and cellular immune systems in elderly asthmatics.

In the present study, humoral and cellular immune responses were examined in elderly patients with bronchial asthma.

Subjects and Methods

Fifteen asthma patients over the age of 70 (9 females and 6 males) were selected for this study (older asthmatics : OA). The mean age was 74.7 years with a range of 70 to 83 years. Fifteen healthy subjects over age 70 (11 females and 4 males, mean age 76.1 years, range 70–87 years) (older healthy subjects : OH) as the controls of older asthmatics and 15 asthmatics under the age of 40 (12 females and 3 males, mean age 25.6

years, range 14–37 years) (younger asthmatics : YA) as the controls of older subjects were selected in this study.

Delayed skin reaction was observed by intradermal injection with 0.02ml of commercial Candida allergen extract and with 0.1ml of PPD. The diameters of induration and flare at 48 h were measured in millimeters after the test. Induration or flare larger than 10mm in the mean of two different diameters was regarded as positive.

IgE antibodies to house dust mite (HDm) and *Candida albicans* were evaluated by radioallergosorbent test (RAST). IgG₄ antibodies to HDm and *Candida albicans* were measured by an indirect enzyme-linked immunosorbent assay (ELISA) by the method (18–20) modified from that described by Engvall et al (21). Serum IgE level was estimated by radioimmunosorbent test (RIST). The serum levels of IgG, IgA, and IgM were measured by turbidometric immunoassay (TIA), and the level of IgG₄ was measured by a method of ELISA.

Results

The level of serum IgE in older asthmatics over the age of 70 (group OA) was significantly higher than that in older healthy subjects over age 70 ($p < 0.01$). The serum IgE level was significantly lower in subjects of group OH than in younger asthmatics (group YA) ($p < 0.001$). There was no significant difference in serum IgE levels between younger and older asthmatics (Table 1).

Table 1. Comparison of serum IgE levels among younger asthmatics, older asthmatics, and older healthy subjects

Study group	No of subjects	Serum IgE levels (IU/ml) Mean \pm SD	Range
YA	15	786 \pm 610 ^a	106-2012
OA	15	558 \pm 650 ^b	10-2007
OH	15	44 \pm 47 ^{bc}	0- 179

YA: younger asthmatics; OA: older asthmatics; OH: older healthy subjects. a, $p < 0.001$; b, $p < 0.01$.

The proportion of subjects with IgE antibodies to house dust mite (HDm) was very low in older asthmatics compared with younger asthmatics. There was no case with IgE antibodies to HDm in the older healthy subjects. In contrast, the proportion of subjects with IgE antibodies to *Candida albicans* was similar between younger and older asthmatics. No case showed a positive RAST score of 2+ or more to *Candida albicans* in older healthy subjects (Table 2).

Table 2. The proportion of subjects with IgE antibodies to house dust mite and/or *Candida albicans* in younger asthmatics, older asthmatics, and older healthy subjects

Study group	No of subjects	No of subjects with a positive RAST score House dust mite	<i>Candida albicans</i>
YA	15	11 (73.3%)	2 (13.3%)
OA	15	1 (6.7%)	3 (20.0%)
OH	15	0 (0%)	0 (0%)

YA: younger asthmatics; OA: older asthmatics; OH: older healthy subjects

Serum IgG level was increased in asthmatic (1504mg/dl) and healthy subjects (1650mg/dl)

in the elderly compared with younger asthmatics (1370mg/dl). However, there was no significant difference between younger and older subjects. No significant difference was found between asthmatic and healthy subjects in the elderly. Serum IgA levels were also higher in asthmatic (311mg/dl) and healthy subjects (264mg/dl) in the elderly than in younger subjects (222mg/dl), although the differences were not significant between younger and older subjects, and between asthmatic and healthy subjects in the elderly. The level of serum IgM was significantly lower in asthmatic (113mg/dl) ($p < 0.01$) and healthy subjects (155mg/dl) ($p < 0.05$) in the elderly than in younger asthmatics (222mg/dl). There was no significant difference between asthmatic and healthy subjects in the elderly (Fig. 1).

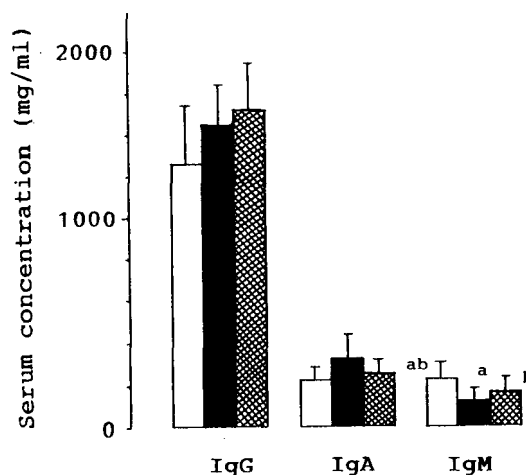


Fig. 1. Comparison of serum concentrations of IgG, IgA, and IgM among younger asthmatics (□), older asthmatics (■) and older healthy subjects (▨). a, $p < 0.01$; b, $p < 0.05$.

The mean level of serum IgG₄ was highest in older asthmatics, and the level over 100mg

/dl was found in 4 of the 14 (28.6%) older asthmatics. In contrast, one subject of 13 younger asthmatics and none of 14 older healthy subjects showed the level of serum IgG₄ over 100mg/dl. There was, however, no significant difference between younger and older asthmatics, and between asthmatic and healthy subjects in the elderly (Fig. 2).

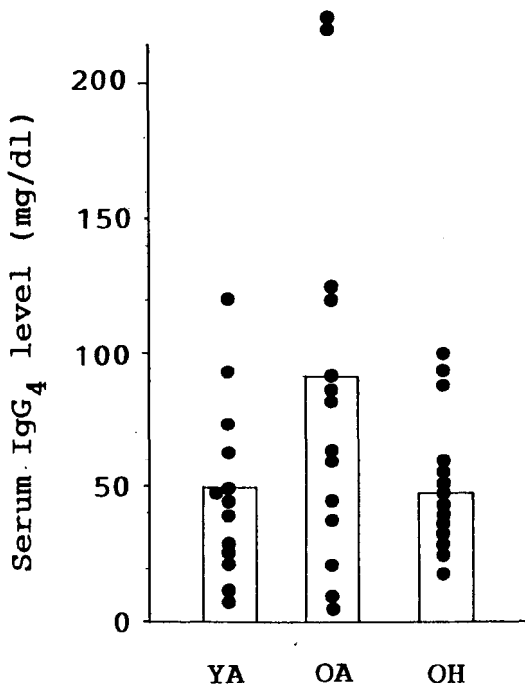


Fig. 2. Comparison of serum IgG₄ concentrations among younger asthmatics (YA), older asthmatics (OA), and older healthy subjects (OH). Vertical columns represent the mean for each group. YA : younger asthmatics ; OA : older asthmatics ; OH : older healthy subjects.

Serum concentrations of IgG₄ antibodies to HDm was not different between younger and older asthmatics, and between asthmatic and healthy subjects in the elderly. In contrast,

the concentration of IgG₄ antibodies to *Candida albicans* was significantly higher in older asthmatics ($p < 0.01$) and older healthy subjects ($p < 0.01$) than in younger asthmatics (Table 3).

Table 3. Serum concentration of IgG₄ antibodies to house dust mite and *Candida albicans* in younger asthmatics, older asthmatics, and older healthy subjects

Study group	No of subjects	Serum concentration of IgG ₄ House dust mite	Serum concentration of IgG ₄ <i>Candida albicans</i> (U/ml)
YA	13	0.37 ± 0.11 ^a	5.9 ± 5.1 ^{ab}
OA	14	0.37 ± 0.11	25.0 ± 22.3 ^a
OH	14	0.44 ± 0.31	27.4 ± 24.6 ^b

^a Mean ± SD. YA: younger asthmatics; OA: older asthmatics; OH: older healthy subjects. a, $p < 0.01$; b, $p < 0.01$.

The proportion of subjects with positive delayed skin reaction to *Candida albicans* was low in older asthmatics compared with younger asthmatics. The number of subjects with positive skin reaction to PPD was also found to be decreased in older asthmatics than in younger asthmatics and older healthy subjects (Fig. 3). The mean diameter of induration by PPD was significantly decreased in older asthmatics compared with that in older healthy subjects ($p < 0.05$) and younger asthmatics ($p < 0.05$). The flare reaction by PPD was also significantly decreased in older asthmatics compared with older healthy subjects ($p < 0.05$). However, there was no significant difference in the mean diameters of induration and flare by *Candida albicans* among the three groups (Table 4).

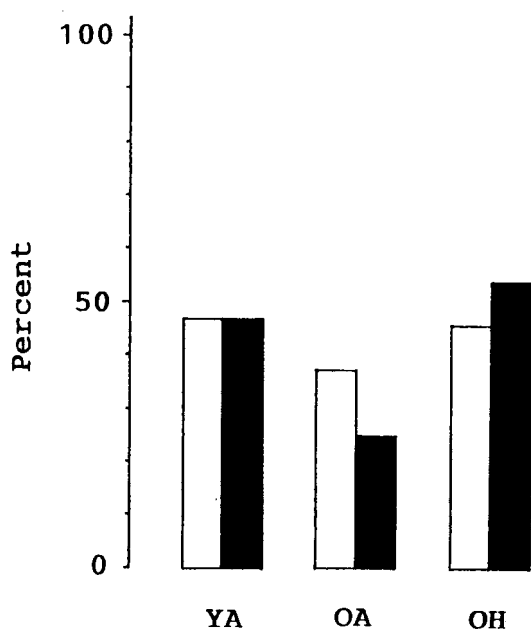


Fig. 3. The proportion of patients showing a positive skin reaction to *Candida albicans* (□) and to PPD (■) in younger asthmatics (YA), older asthmatics (OA), and older healthy subjects (OH). Vertical columns represent the mean for each group.

Table 4. Mean diameters of induration and flare reaction to *Candida albicans* and PPD

Study group	No of subjects	Induration		Flare	
		<i>Candida</i>	PPD	<i>Candida</i>	PPD
YA	13	7.8±4.2*	7.7±5.2 ^a	19.1±13.2	14.0±13.1
OA	8	5.6±3.6	2.8±3.8 ^{ab}	8.9± 9.6	5.1± 5.2 ^c
OH	11	6.5±3.6	7.7±4.2 ^b	11.5±11.6	16.8±15.0 ^c

* Mean ± SD. YA: younger asthmatics; OA: older asthmatics; OH: older healthy subjects. a, b, and c, $p < 0.05$.

Discussion

Bronchial asthma is characterized by bronchial hyperresponsiveness, mainly related to

IgE-mediated immune response (22). IgE-mediated immune response is shown to be predominant among children and young adult asthma patients, while the reaction is not found in some older asthma patients. Thus, it has been widely accepted that there are clear differences between allergic (extrinsic) and nonallergic (intrinsic) types of asthma, based on the presence or absence of an increased concentration of serum IgE (23). However, Burrows et al. have reported that asthma is almost always associated with some type of IgE-related reaction (22). It is a difficult problem to clarify whether IgE-mediated reaction participates in all asthma patients.

In addition to IgE mediated immune reaction, participation of IgG antibodies, particularly IgG₁ and IgG₄ in the mechanism of onset of asthma has been noted. IgG₄ was at first identified as the blocking antibody for IgE-mediated immune response (6). Later, several investigators have demonstrated that the rise of IgG₄ antibodies is associated with unfavorable prognostic criterion (7-9). Thus, the role of IgG₄ antibodies is now controversial.

In recent years, the number of elderly patients with bronchial asthma has been increasing. There are, however, few reports about the feature of humoral and cellular immune system in bronchial asthma in the elderly. Our data from this study show that bronchial asthma in the elderly is characterized by two factors: immune response, which is similar to that of young adult patients and aging, which affects immune response. Thus, immune response and aging are influenced elderly asthma patients each other.

An elevated level of serum IgE and the presence of IgE antibodies to HDm and

Candida albicans are representative features of atopic asthma. In contrast, elevation of serum IgG, IgA, decrease in serum IgM, rise of IgG, antibodies to *Candida albicans* and depressed delayed skin reactivity to PPD are considered to be mainly due to aging, since these findings except delayed skin reactivity to PPD were not different between asthmatic and healthy subjects in the elderly. That is, IgE-mediated immune response found in elderly asthmatics is similar to that in younger asthmatics. However, IgG-mediated and cell-mediated immune responses in elderly asthmatics were different from that in younger asthmatics. These features of immune system have to be considered in analysis of the pathology of bronchial asthma in the elderly.

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老年者気管支喘息における液性および細胞性免疫反応について

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気管支喘息における液性および細胞性免疫反応について, 老年者気管支喘息, 老年者健常人, および若年者気管支喘息の間で比較検討を行った。

1. まず, 液性免疫では, 血清IgE値高値, ハウスダストやカンジダに対するIgE抗体陽性などのIgE系反応は, 老年者気管支喘息においては明らかに観察されたが, 老年者健常人では全く観察されなかった。血清IgGおよびIgA値には3者間に有意の差は見られなかったが, 血清IgMは, 若年者喘息に比べ老年者喘息で有意に低い

値を示した。

2. ハウスダストやカンジダに対するIgE抗体は老年者喘息において老年者健常人に比べより高い頻度で陽性であったが, 一方, ハウスダストに対するIgG₄抗体は3者間に有意の差は見られなかった。また, カンジダに対するIgG₄抗体は, 老年者喘息および健常人において, 若年者喘息に比べ有意の高値を示した。しかし, 老年者の喘息と健常人との間には有意の差は見られなかった。

3. PPDによる遅延型皮膚反応は, 若年者喘息に比べ老年者喘息において有意の減弱傾向を示した。

これらの結果は, 老年者喘息はIgE系反応を有していること, そして, 加齢による免疫反応の変化の影響を受けること, を示している。

キーワード: IgE, IgG₄, 免疫グロブリン, 気管支喘息, 加齢