◎原 著

Cell-mediated immunity in bronchial asthma. Depressed response towards Candida albicans

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Abstract : Delayed cutaneous hypersensitivity towards Candida albicans was examined in 200 patients with bronchial asthma in relation to patient age and the level of total IgE.

1. Delayed skin reactivity towards C.albicans was depressed in the patients between the ages of 10 and 20 and in those over the age of 61. A significant difference was present in delayed skin reactivity between the groups of 10−20 and 41−50 years old.

2. The frequency of the patients with positive delayed skin reactivity towards C.albicans was the highest in those with low levels of total IgE (0−100 IU/mℓ) and the low est in those with high levels of total IgE (over than 1001 IU/mℓ).

The results suggest that cell-mediated immunity towards C.albicans is depressed re lating to atopics in the patients between 10 and 20 and to aging in the patients over 61.

Key words : cell-mediated immunity, bronchial asthma, atopics, aging

In has been shown that immediate immune response mediated by IgE plays an important role in the onset mechanism of bronchial asthma[1~3]. Patients who have IgE-mediated immune response causing asthma attacks are evaluated as atopic[4, 5]. In some atopic patients delayed immune response has been suggested to be depressed. The increased production of specific antibodies[6] and diminished delayed skin reaction[7, 8] are observed in the immune response of some atopics towards Candida albicans. The depressed delayed immune response leads to saprophytic C.albicans growth, which accelerates the production of specific IgG antibody[9, 10], because in defence against C.albicans the cell-mediated immune system plays the major role[11].

In the present study delayed cutaneous hypersensitivity towards C.albicans was observed in patients with bronchial asthma in

relation to patient age and the level of total IgE.

Subjects and Methods

The subjects were 200 patients (113 felmales and 87 males) with bronchial asthm. Their mean age was 36.7 years with a range of 10 to 76 years. The subjects were divided into six groups 10−20, 21−30, 31−40, 41−50, 51−60, and 61+ years of age, and also divided into five groups, 0−100, 101−300, 301−700, 701−1000 and 1001+IU/mℓ, according to the level of total IgE in sera.

Intradermal skin test was performed with 0.02mℓ of commercial Candida allergen extract (Torii Co, Japan). The diameters of flare and wheal at 20 min, and flare and induration at 48 hr were measured in millimeters after the test. The diameter of flare larger than 20mm or wheal larger than 9mm was regarded as positive in immediate skin reaction. Flare or induration larger than 10mm in diameter was regarded as positive in delayed skin reaction.

In this study, house dust, ragweed, buckwheat, Aspergillus, Alternaria, Cladosporium and Candida albicans extracts were used for immediate skin reaction to assess the subjects as atopic. Specific IgE antibodies towards house dust and C.albicans were examined by a radioallergosorbent test (RAST). The subjects with positive skin reaction towards the allergens except C.albicans and/or with positive RAST towards house dust or C.albicans were regarded as atopic. The level of total IgE in sera was measured by a radioimmunosorbent test (RIST).

Results

1. Characteristic of subjects studied

The ferquency of atopic asthmatics was the highest in the patients between 10 and 20, in which thirty nine (97.5%) of the 40 subjects were atopic, and the lowest in those over age 61, showing 14.3% in the frequency.

2. Delayed skin reaction and patient age.

Immediate skin response towards C.albicans was positive in 60.0% to 71.4% among the six age groups. Any difference was not found in positive immediate skin response among them. The frequency of the patients with positive delayed skin reaction towards C.albicans was the highest (62.5%) in the patients between 41 and 50, and the lowest (30.0%) in those between 10 and 20. A significant difference was found in the delayed skin reaction between the two groups ($p<0.001$). The frequency of the patients showing positive delayed skin reaction towards C.albicans tended to decrease with aging after 51 years old. The frequency was 42.8% in the patients over age 61. No significant difference was, however, present between the patients aged 41 to 50 and those over age 61 (Fig. 1).

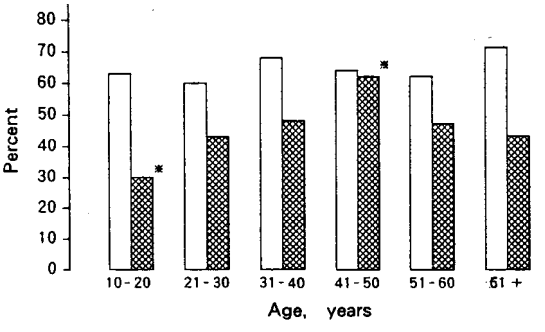

Fig. 1. Frequency of cases with positive immediate (□) and delayed (▨) skin reaction to Candida albicans in relation to patient age. *Significant difference at $P<0.001$.

3. Delayed skin reaction and serum IgE level

Delayed skin response towards C.albicans was the most frequently positive (66.7%) in the patients whose level of total IgE was low (0 to 100 IU/mℓ). The frequency of the patients showing positive delayed cutaneous hypersensitivity towards C.albicans was the lowest in those with a higher level of total IgE (more than 1001 IU/mℓ). The difference was significant between the patients with low and high levels of total IgE ($p<0.05$) (Fig. 2).

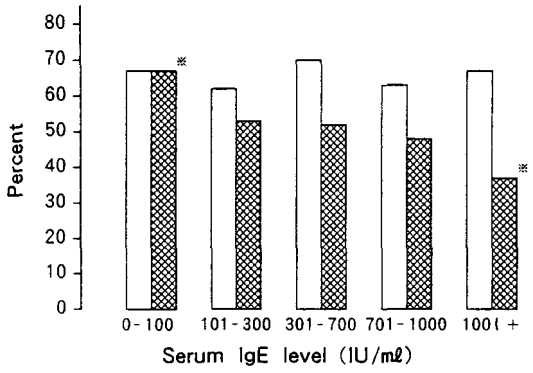

Fig. 2. Frequency of cases with positive immediate (□) and delayed (▨) skin reaction to Candida albicans in relation to serum IgE level. *Significant difference at $P<0.05$

Discussion

Candida albicans-induced asthma has been suggested to be complicated and different from asthma elicited by house dust mite[12~14]. On bronchial challenge with C.albicans, immediate asthmatic response (IAR), often late asthmatic response (LAR) and sometimes delayed response can be observed. These phenomena are thought to be associated with specific IgG antibodies, which are predominantly produced by sensitization with C.albicans. The cell-mediated immunity acts to make a defense against invasion of C. albicans. The defect of cell-mediated immunity primarily cause saprophytic C.albicans growth. Therefore, the increased production of specific IgG antibodies against C.albicans has been proposed to be due to depressed cell-mediated immune response[9, 10].

It has been reported that the depressed cell-mediated immune response can be observed in some atopic subjects[7, 8]. In the present study delayed skin reactivity towards C. albicans was significantly decreased in the patients between 10 and 20, the majority of whom were atopic, and in those with high level of total IgE. It might be speculated that the cell-mediated immune response is depressed in atopic subjects, associated with IgE antibodies. In the patients over age 61, diminished cell-mediated immunity was also found, suggesting that cell-mediated immune system might be depressed with aging.

Furthermore, an increase in specific IgG_4 antibodies against C.albicans could be observed in patients with steroid-dependent intractable asthma[15]. This might be due to depressed cell-mediated immunity caused by long-term regimen of glucocorticoid hormone.

These findings show that suppression of cell-mediated immune response can be observed in atopic subjects, elderly subjects and subjects with long-term corticosteroid therapy, and that in these conditions production of specific IgG antibodies is predominantly increased, leading to complicated onset mechanism of bronchial asthma.

References

1. Ishizaka T, Ishizaka K, Conrad DH. Froese A. A new concept of mechanisms of IgE-mediated histamine release. J Aller-

gy Clin Immunol 64 : 320−236, 1978.
2. Ishizaka T, Hirata F, Ishizaka K, Axelrod, J. Stimulation of phospholipid methylation, Ca^{2+} influx and histamine release by bridging of IgE receptors on rat mast cells. Proc Natl Acad Sci USA 77 : 1903−1906, 1980.
3. Ishizaka T, Foreman JC, Sreak AR, Ishizaka, K. Induction of calcium uptake across the rat mast cell membrane by bridging IgE receptors. Proc Natl Acad Sci USA 76 : 5858−5862, 1979.
4. Tanizaki Y, Komagoe H, Morinaga H, Kitani H, Goda Y, Kimura I. Allergen- and anti-IgE-induced histamine release from whole blood. Int Archs Allergy Appl Immunol 73 : 141−145, 1984.
5. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kitani H, Nakagawa S, Takahashi K, Kimura I. Reactivity of sensitized human basophils, as expressed by histamine release. Jpn J Allergol 33 : 463−468, 1984.
6. Pepys J, Faux JA, Longbottom JL, McCarthy DS, Hargreave FE. Candida albicans precipitins in respiratory disease in man. J Allergy 41 : 305−317, 1968.
7. Elliot ST, Hanifin JM. Delayed cutaneous hypersensitivity and lymphocyte transformation. Arch Dermatol 115 : 36−39, 1979.
8. McGeady SJ, Buckley R H. Depression of cell-mediated immunity in atopic eczema. J Allergy Clin Immunol 56 : 393−406, 1975.
9. Savolainen J, Viander M, Koivikko A. IgG antibody responses to carbohydrate and protein antigens of Candida albicans in asthmatic children. Allergy 45 : 54−63, 1990.
10. Savolainen J, Koivikko A, Kalimo K, Nieminen E, Viander, M. IgE, IgA and IgG antibodies and delayed skin response towards Candida albicans antigens in atopics with and without saprophytic growth. Clin Exp Allergy 20 : 549−554, 1990.
11. Rogers TI, Balish E. Immunity to Candida albicans. Microbiol Rev 44 : 660−682, 1980.
12. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kitani H, Nakagawa S, Matsuoka T, Tada S, Takahashi K, Kimura I. Candida-induced histamine release from basophils : Relationship to house dust- and anti-IgE-induced secretion. Acta Med Okayama 39 : 191−197, 1985.
13. Tanizaki Y, Komagoe H, Sudo M, Kitani H, Nakagawa S, Tada S, Takahashi K, Kimura, I. Basophil histamine release induced by Candida albicans. Relation to specific IgE and IgG antibodies. Jpn J Allergol 34 : 422−427, 1985.
14. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kitani H, Kimura I. Comparison of basophil histamine release induced by the cross-linking of IgE receptors. Acta Med Okayama 39 : 441−446, 1985.
15. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Takatori A, Okuda H, Harada H. Candida specific IgG_4 antibodies and bronchial asthma. Papers of the Institute for environmental Medicine, Okayama University Medical School. 62 : 4, 1991.

気管支喘息患者における細胞性免疫，ガンジダ抗原に対する遅延型反応の抑制

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気管支喘息200例を対象にカンジダに対する即時型および遅延型皮膚反応を観察し，これらの皮膚反応と年令，血清IgE値との関連について検討を加えた。

1. カンジダに対する遅延型皮膚反応は，10～20才の年齢層および61才以上の年齢層の症例において，その陽性率の低下が観察された。そして，10～20才の年齢層と41～50才の年齢層の症例では，両者間で陽性率の有意の差が見られた($p<0.001$)。

2. カンジダに対する遅延型皮膚反応の陽性率は，血清IgE値が低い（0～100 IU／mℓ）症例において最も高く，一方血清IgE値が高い（1001 IU／mℓ以上）症例において最も低いという傾向が見られた。

これらの結果は，カンジダに対する細胞性免疫は，10～20才の年齢層ではアトピーと，また61才以上の年齢層では加齢と関連して抑制されることを示唆するものと考えられる。

キーワード：細胞性免疫，カンジダ，気管支喘息，アトピー，加齢