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Chronological Changes in Serum IgG4 in Asthmatic Patients and the Relationship with IgE

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Summary

Changes with time and seasonal changes in serum levels of IgG4 antibody (IgG4) in patients with bronchial asthma were studied. In addition, the relationships with serum IgE antibody (IgE) levels and with oral glucocorticoid preparations (CS preparations) used for treatment were also examined.

The subjects of this study were 50 patients with bronchial asthma who had undergone at least two examinations in the 9-year period between 1986 and 1994. They consisted of 27 patients (group A) with atopic asthma who were positive for house dust (HD) and *Dermatophagoides farinae* (DF), and 23 patients (group NA) who had negative non-atopic asthma.

Serum total IgG4 (T-IgG4), and HD-specific and DF-specific IgG4 antibodies (HD-IgG4 and DF-IgG4) were measured using ELISA. Serum total IgE (T-IgE) was measured by the radioimmunosorbent test (RIST), and HD-specific and DF-specific IgE antibodies (DH-IgE and DF-IgE) were measured by the radioallergosorbent test (RAST).

In chronological studies, T-IgG4 varied basically within the normal range in both group A and NA. T-IgE increased from the beginning and continued to increase in 20 patients in group A. HD-IgG4 increased and this increase continued in about half of the patients in groups A and NA, but variations among patients were observed. DF-IgG4 showed increases in 12 patients in group A, persisting in 10 patients. In group NA, increases were found in two CS-dependent patients.

Concerning seasonal changes, T-IgE increased only in the autumn and not in any other seasons in two patients with atopic dermatitis in group A.

In both groups A and NA, the levels were basically constant in each patients, and no changes with time or season were observed.

IgE and IgG4 production is controlled by various cytokines, but both IgE and IgG4 appear to undergo a class switch by interleukin 4 and interleukin 13. The present results indicated that the antibody production was basically constant in individual patients with no change with time or by season and with little effect caused by CS preparation.

Introduction

The relationship between immunoglobulin E (IgE) and another immunoglobulin was observed in

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Table 1. Patient profile

Bronchial ashma :	50 cases (♂ 23 ♀ 27)
Onset age	2～69 y.o. (Avg. 28.4±19.7)
Age (first examination)	16～72 y.o. (Avg.40.7±16.0)
Type : atopic	27 cases (♂ 18 ♀ 9)
non-atopic	23 cases (♂ 5 ♀ 18)

	Atopic	Non-atopic
Number	27 cases	23 cases
Onset age	2～69 y.o. (Avg. 17.3±16..9)	3～63 y.o. (Avg. 41.5±14.2)
Age (first examination)	16～72 y.o. (Avg. 33.7±14.6)	22～71 y.o. (Avg. 48.8±13.6)
Nasal Allergy	4	4
Atopic Dermatitis	2	1
Therapy		
Bronchodilator		
Theophyllin	24(5)	20(3)
β-stimulant (p.o.)	20(11)	16(7)
(inh.)	21(2)	19(5)
Anti-allergic agent	24(7)	20(1)
Corticosteroids (p.o.)	7(2)	9((0)
(inh.)	11(1)	14((2)
Severity (Japan Allergic Society)		
Mild Step 1	14	6
Moderate Step 2	8	6
Step 3	2	3
Severe Step 4	3	8

allergic diseases. Immunoglobulin G (IgG), especially subclasses IgG1 and IgG4 were studied. At the beginning of these studies, IgG4 antibody indicated reaginic-like antibodies[1], but allergen-specific IgG4 antibodies in serum which increased in the course of immunotherapy were considered to be blocking antibodies[2)~4)].

Chronological and seasonal changes in serum of IgG4 antibody (IgG4) in patients with bronchial asthma were studied. In addition, the relationships with serum IgE antibody (IgE) levels and also with oral glucoocorticoid preparations (CS preparations) used for treatment were examined.

Subjects

The subjects of this study were 50 patients with bronchial asthma who had undergone at least two examinations in the 9-year period between 1986 and 1994. They were examined for total IgG4 (T-IgG4), house dust specific IgG4 (HD-IgG4), dust mite, *Dermatophagoides farinae*, specific IgG4 (DF-IgG4), and they recieved no immunotherapy for house dust (Table 1).

The ages of the patients at the onset of disease were 2 to 69 (28.4 on average) and the ages at the first examination were 16 to 72 (40.7 on average). Types of asthmatics were defined by RAST (Radioallergosorbent test) ; atopic asthma (group A) showed positive HD or DF-IgE (0.7 PRU/ml<), and non-atopic asthma (group NA) showed negative HD or DF-IgE (0.69 PRU/ml>). They consisted of 27 patients in group A, and 23 patients in group NA. Age at onset and the first examination, treatment and degree of severity according to the Japan Allergy Society are shown in Table 1. Oral glucocorticoid preparations (CS preparation) used for treatment in 5 cases of 5-10 mg daily in group A, and 9 cases

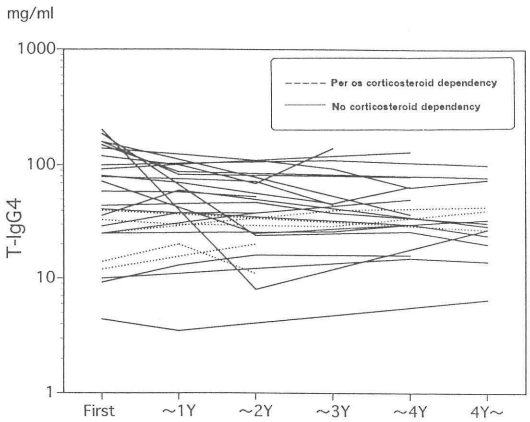

Fig. 1 Change of total IgG4 in group A

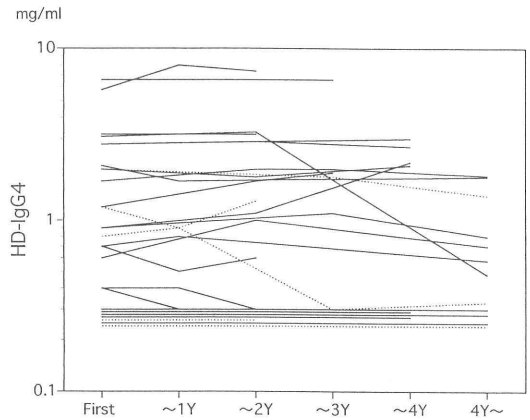

Fig. 2 Change of HD-IgG4 in group A

of 5 to 15 mg daily in group NA. The doses of other CS preparations (betamethasone, paramethasone) were converted into prednisolone dose equivalents. The changes from the initiation of the study were observed and the data were divided according to the 4 seasons and seasonal changes were compared.

Methods

Assay

1) Serum T-IgG4, HD-IgG4 and DF-IgG4

Concentration were determined by ELISA as previously described[5] using monoclonal antibodies (Yamasa Co. Ltd, Tokyo). To determine HD and DF-IgG4, HD and DF extracts (Torii Phamceutical Co. Tokyo) were added. In healthy volunteers, the normal value of T-IgG4 was 6-140 mg/dl, that of HD-IgG4 was less than 2.0 U/ml, and that of DF-IgG4 was under 0.3 U/ml.

2) Serum T-IgE, HD-IgE and DF-IgE

T-IgE was determined by RIST (radiommunosorbent test) ; HD (Hollister-Stier Lab. Washington) and DF (Pharmacia, Uppsala, Sweden) IgE was determined by RAST (radioallergosorbent test), partially by CAP-RAST (both Pharmacia).

The normal value of T-IgE was less than 250 IU/ml and those of HD and DF-IgE were under 0.7 PRU/ml.

Statistics

Immunoglobulin concentrations were log transformed. Geometric means were compared by Student's t-test and paired t-test.

Results

Time course changes

1) Atopic asthmatics (group A)

In 27 patients, T-IgG4 incerased from the beginning in 4 cases, but they later returned to the normal range. T-IgG4 varied within the normal range in many cases, including CS-dependent cases (Fig. 1). T-IgE increased in 20 cases from the beginning, and these patients continued to show high T-IgE levels, with or without CS dependency.

HD-IgG4 increased in 7 cases, and 5 of these continued to show high HD-IgG4 levels (Fig. 2). HD -IgE initially increased in 22 cases, and also increased in the other 5 cases during the course of the study.

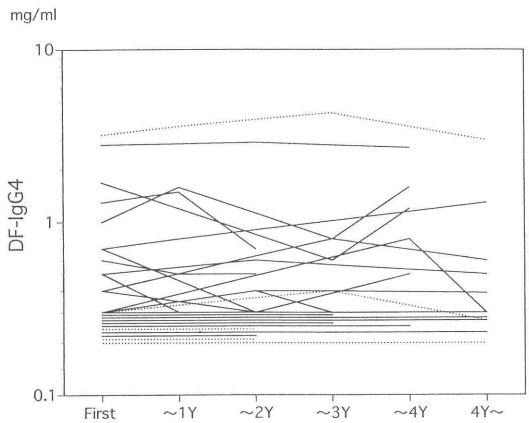

Fig. 3 Change of DF-IgG4 in group A

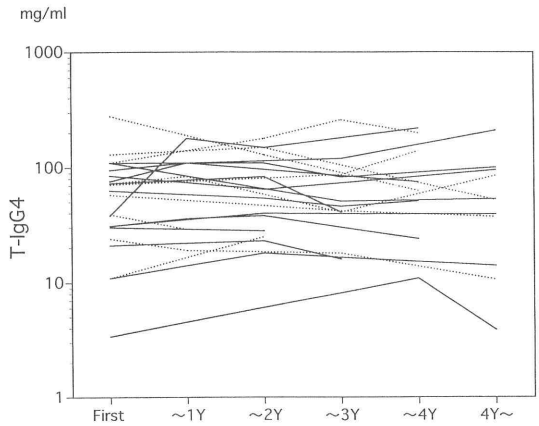

Fig. 4 Change of total IgG4 in group NA

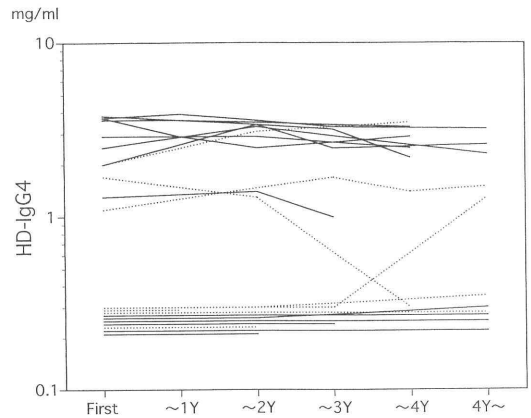

Fig. 5 Change of HD-IgG4 in group NA

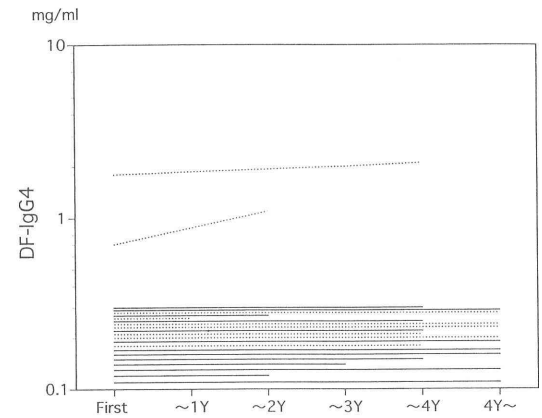

Fig. 6 Change of DF-IgG4 in group NA

DF-IgG4 initially increased in 12 cases, and all but one of these patients continued to show high DF-IgG4 levels. Fifteen cases were in the normal range at the beginning, but later increased in 3 cases (Fig. 3). DF-IgE initially increased in 25 cases, including 2 CS-dependent cases.

2) Non-atopic asthmatics (group NA)

In 23 patients, T-IgG4 did not change except in 2 cases, including CS-dependent cases (Fig. 4). T-IgE increased in 2 CS-dependent cases initially, but both returned to the normal range.

HD-IgG4 increased in 6 cases, who continued to show high HD-IgG4 levels, while 2 cases initially in the normal range later increased (Fig. 5). HD-IgE was in the normal range continuously in all cases. DF-IgG4 was elevated and remained in 2 CS-depndent cases (Fig. 6). DF-IgE was always in the normal range in all cases.

3) The IgG4/IgE ratio

In group A, the T-IgG4/T-IgE ratio did not change. The HD-IgG4/HD-IgE ratio fell over the 4 years compared with the beginning ($p<0.05$). The DF-IgG4/DF-IgE ratio did not change (Fig. 7).

In group NA, the T-IgG4/T-IgE ratio did not change. The HD-IgG4/HD-IgE ratio and the DF-IgG4/DF-IgE ratio also did not change (Fig. 7).

Seasonal changes

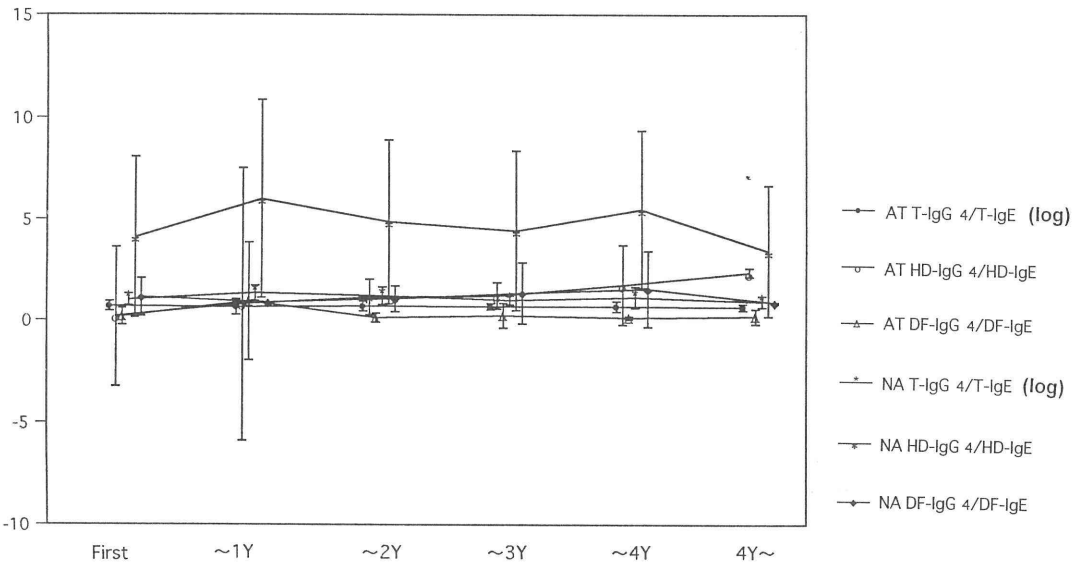

Fig. 7 Change of IgG4/IgE ratio in groups A and NA

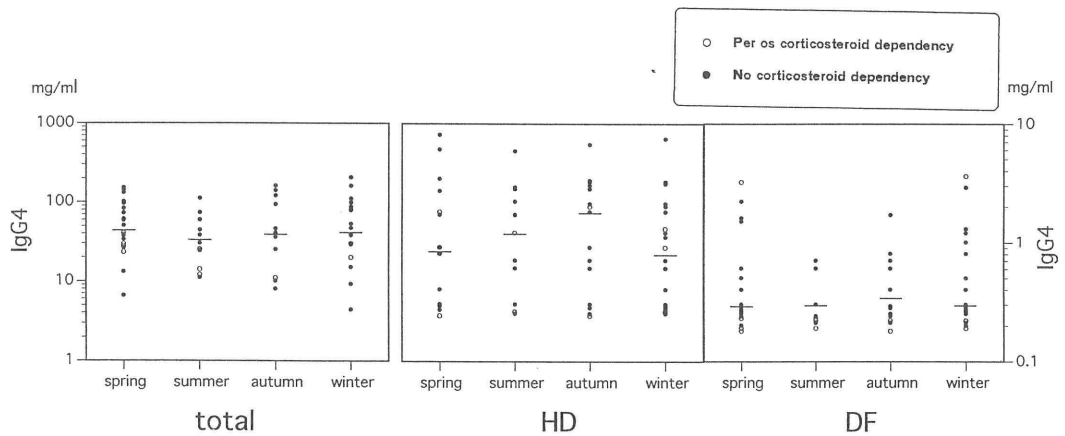

Fig. 8 Seasonal comparison of IgG4 in group A

1) Atopic asthmatics (group A)

In 27 cases, T-IgG4 tended to fall in the summer, but it remained in the normal range (Fig. 8), and T-IgE did not change except in 2 cases associated with atopic dermatitis, who showed greater elevation in autumn. HD-IgG4 increased in 6 cases, without any relationship to the season (Fig. 8), while HD-IgE increased in autumn and winter in 4 cases who were in the normal range in other seasons. In the autumn, DF-IgG4 increased in 3 cases (Fig. 8), and DF-IgE fell in some cases in the spring and autumn, but the average did not change seasonally.

2) Non-atopic asthmatics (group NA)

In 23 patients, T-IgG4 increased in 4 cased but the average did not change seasonally (Fig. 9), and T-IgE tended to increase in the spring and summer but the average did not change seasonally. In all cases HD-IgG4 did not change seasonally but increased slighty on average in the summer (Fig. 9), HD -IgE did not change seasonally. DF-IgG4 increased in 2 cases without any seasonal relation (Fig. 9), and

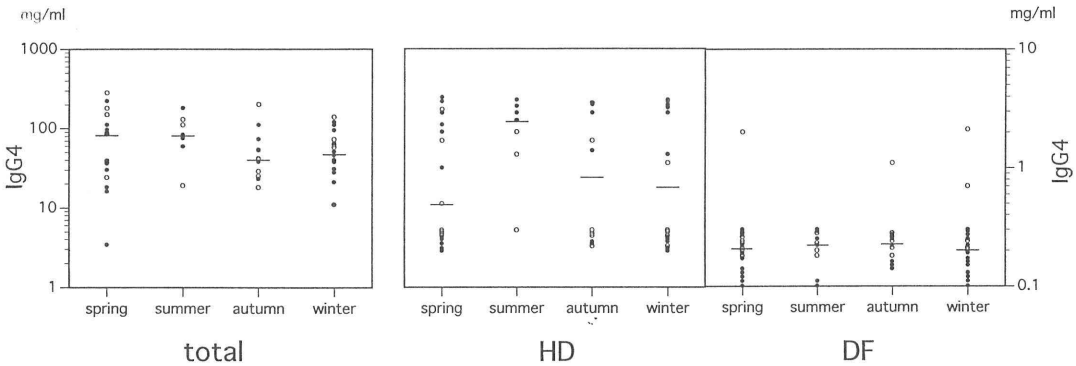

Fig. 9 Seasonal comparison of IgG4 in group NA

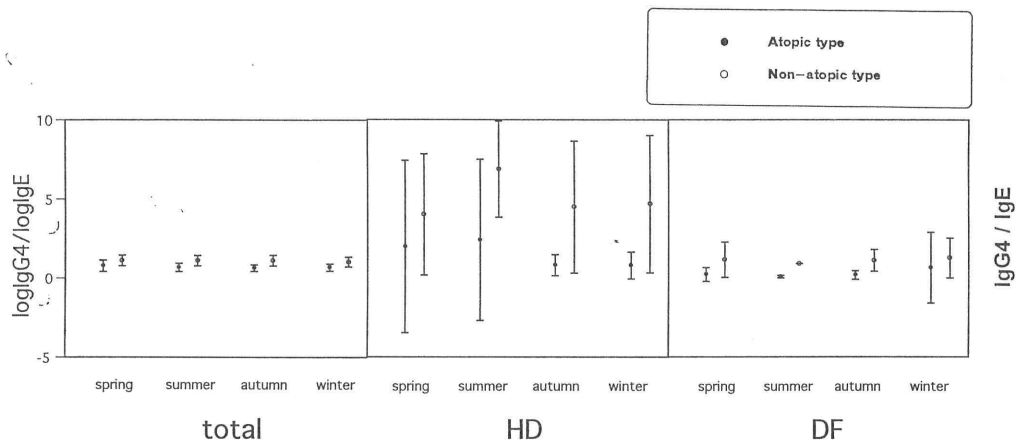

Fig. 10 Seasonal comparison of IgG4/IgE ratio in groups A and NA

DF-IgE did not change seasonally.

3) The IgG4/IgE ratio

In group A, the T-IgG4/T-IgE ratio did not change (Fig. 10). The HD-IgG4/HD-IgE ratio and the DF-IgG4/DF-IgE ratio did not change seasonally (Fig. 10).

In group NA, the T-IgG4/T-IgE ratio did not change (Fig. 10). The HD-IgG4/HD-IgE ratio differed in spring and summer in average, but it was not shown to be significant by the paired t-test. The DF-IgG4/DF-IgE ratio did not change seasonally (Fig. 10).

Discussion

The IgG4 isotype is the least abundant IgG subclass in man and represents approximately 4% of total IgG in serum in the adult. IgG4 antibodies do not behave as innocent bystanders with respect to complement activation caused by other isotypes. A small part of the IgG4 subclass probably can bind to basophil and mast cells, but IgG4 antibodies usually do not behave as anaphylactic antibodies[6].

We reported that the DF-IgG4 level tended to increase after 3-6 months of HD immunotherapy. In that study, we found a natural elevation of DF-IgG4 in atopic asthmatics, especially in high HD and DF RAST score patients aged less than 15 at onset, and a few non-atopic asthmatics[7].

In this study, the chronological changes and seasonal changes of IgG4 and IgE in patients of bronchial

asthma were studied.

T-IgG4 varied within the normal range, with or without oral CS preparation in both types. T-IgE was elevated in group A, and in 2 cases with atopic dermatitis showed more elevation in the autumn. Many cases of atopic dermatitis sensitized by many allergens involved HD and DF. We considered that elevation of T-IgE in autumn was related to the amount of enviroment allergens. In group A, the class switch of IgG4 to IgE were accelarated. In many cases of both types, T-IgG4 and T-IgE were fixed, and in all cases the regulation of production did not change.

HD-IgG4 was elevated in about half of both types continuously. HD extract was a mixture of many allergens, in group NA we considered the relation of *Candida albicans* (data not shown).

DF-IgG4 increased continuously in group A, therefore the acceleration of class switch to both DF-IgG4 and DF-IgE was considered. In group NA, only 2 CS dependent cases were elevated. The relation of IgG4 and late asthmatic response must be considered[8].

Increased IgG4 antibody in cases recieving immunotherapy was considered to be a blocking antibody, but the significance of differences in IgG4 value among untreated patients was unclear. The structural differences between the heavy polypeptide chains of the human IgG4a and IgG4b subtypes would be expected to be small[9].

Recently interleukin 4 (IL-4) was shown to induce IgG4 and IgE switching[10] and interleukin 13 (IL-13) also induces IL-4 independent IgG4 and IgE synthesis[11].

From the present results, in both group A and NA, the levels were basically constant in all patients, and no chronological or seasonal changes were observed. IgE and IgG4 production is controlled by various cytokines, but both IgE and IgG4 appear to undergo a class switch by IL-4 and IL-13.

In group A, 20 cases showed normal T-IgG4 levels but high T-IgE levels. The T-IgG4/IgE ratio was different in normal T-IgE group and high T-IgE group ($p<0.0001$). Concerning this differnce, the possibility of the differnce of the sensitibity of B lymphocytes to IL-4 and IL-13 was considerd. And CD40 ligand of T lymphocyte was important in the proliferation of B lymphocyte and the class switching, the difference of CD40 ligand was also considerd.

The present results indicated that the antibody production was basically constant in individual patients with almost no changes with time or season and with little effect by CS preparation.

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気管支喘息患者血清 IgG4 の経時的観察と IgE との関連

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気管支喘息患者血清中 IgG4 抗体(IgG4) の経時的変化と季節的変化を検討した．また同時に血清中 IgE 抗体（IgE）との関連，治療のなかの経口副腎皮質ステロイド剤（CS 剤）との関連についても検討した．

対象は 1986 年から 1994 年の 9 年間，2 回以上の検査を受けた気管支喘息患者 50 名で，ハウスダスト(HD)，コナヒョウヒダニ（DF）に陽性を示すアトピー型喘息（A 群）27 例と，陰性の非アトピー喘息（NA 群）23 例である．

血清総 IgG4 (T-IgG4)，HD および DF 特異 IgG4 抗体 (HD-IgG4，DF-IgG4) は ELISA 法で測定した．血清総 IgE (T-IgE) は RIST (Radioimmunosorbent test) で，HD および DF 特異 IgE 抗体（HD-IgE，DF-IgE）は RAST (Radioallergosorbent test) で測定した．

経時的変化では T-IgG4 は A 群，NA 群ともほぼ基準値内での変動であった．T-IgE は A 群で 20 例初回時より上昇しており上昇は持続した．HD-IgG4 は A 群，NA 群とも約半数が上昇しており，上昇は持続したが変動がみられた．DF-IgG4 は A 群で 12 例上昇がみられ，10 例で上昇が持続した．NA 群では CS 依存の 2 例で上昇がみられた．

季節的変化では，T-IgE が A 群のなかのアトピー性皮膚炎を合併した 2 例で，秋に上昇がみられた以外は変化はなかった．

A 群，NA 群いずれも個々の例でほぼ一定であり，経時的変化，季節的変化を示さないことがわかった．IgE，IgG4 とも種々のサイトカインによって産生調節がされているが，IgE，IgG4 ともインターロイキン 4 およびインターロイキン 13 によりクラススイッチされると考えられており，今回の結果からこれらの産生は個々の例でほぼ一定しており，時間的，季節的変化はみられず，CS 剤による影響も少ないと思われた．

キーワード：気管支喘息，免疫グロブリン G4，特異免疫グロブリン G4，免疫グロブリン E．