◎原 著

Serum cortisol levels in patients with bronchial asthma. Relationship to glucocorticoid therapy and patient age.

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Abstract : Serum cortisol levels were examined in 94 patients with bronchial asthma in relation to dose of glucocorticoids and age. 1. The level of serum cortisol was significantly lower in group A patients, treated with glucocorticoids (prednisolone of 5 mg/day or more) for more than 2 years, (2.4 ± 1.2mcg/dl) than in group B, treated with glucocorticoids (prednisolone of 5 mg or less) for less than 2 years, (6.8 ± 3.7mcg/dl) ($p<0.001$) and in group C, treated without glucocorticoids, (12.6 ± 3.9mcg/dl) ($p<0.001$). The serum cortisol level was also significantly lower in group B than in group C ($p<0.001$). 2. The level of serum cortisol was significantly lower in patients over the age of 70 compared to that in those aged between 0 and 39 years ($p<0.01$) and those between 40 and 49 ($p<0.05$), and those between 50 and 59 ($p<0.02$). The level was also lower in patients between 60 and 69 compared to that in those between 0 and 39, however, this was not significant.

These results demonstrate that the level of serum cortisol decreases by long-term glucocorticoid regimen and with aging.

Key words : serum cortisol level, bronchial asthma, clinical asthma type, glucocorticoids, aging

Introduction

In the onset mechanism of asthma, humoral factors such as histamine and leukotrienes in the early stage of asthma attacks[1,2], and cellular components such as lymphocytes, neutrohils, eosinophils, and basophils in the late stage[3-5] have been shown to play important roles. Particularly in recent years, attension has been focused on

airway inflammation[6-8], since it is closely related to the severity of asthma[9]. In many patients with bronchial asthma, their attacks can be controlled with the usual antiasthma drugs, such as bronchodilators, expectorants, antiallergic agents, and inhalant glucocorticoids. However, there are some asthma patients whose attacks cannot be controlled with conventional antiasthma drugs, and who often require longterm systemic glucocorticoid therapy[10-12]. Although glucocorticoids are effective in severe asthma attacks, the many adverse side effects of these drugs, such as the induction of hypertension, diabetes mellitus, osteoporosis, and muscle weakness, should be considered. Furthermore, the suppression of adrenocortical glands by longterm systemic glucocorticoid regimen, clinically observed as reduced levels of serum cortisol, is important in the treatment of asthma.

In the present study, serum cortisol levels in patients with asthma were examined in relation to dose of glucocorticoids used and patient age.

Subjects and Methods

The subjects were 94 patients with asthma (51 females and 43 males, mean age 53.3 years, range 16−82 years). The subjects were divided into three groups according to dose of glucocorticoids used : patients who had been treated with glucocorticoids for more than 2 years and whose maintenance dose of prednisolone of 5 mg/day or more (group A), those treated with 5 mg/day of prednisolone or less for less than 2 years (group B), and those treated without glucocorticoids (group C). The subjects were further divided into 5 groups according to their age : 0 −39, 40−49, 50−59, 60−69, and 70 + years.

Asthma classification was made according to clinical symptoms based on previously reported criteria[13-15]. Type Ia. Simple bronchoconstriction : patients with symptoms such as wheezing and dyspnea, which are elicited mainly by bronchoconstriction. In this study, this type was further divided into two subtypes according to the amount of expectoration ; type Ia− 1 (0 −49mℓ/day) and type Ia− 2 (50−99mℓ/day).

Type Ib. Bronchoconstriction + hypersecretion : patients with symptoms due to hypersecretion (more than 100 mℓ/day of expectoration), in addition to bronchoconstriction.

Type II. Bronchiolar obstruction : patients with symptoms elicited mainly by bronchiolar obstruction.

Serum cortisol levels were measured by radioimmunoassay (RIA) between 7 : 00 and 8 : 00 a.m. within a few days after the patients were admitted to our hospital.

The level of serum IgE was determined by radioimmunosorbent test (RIST).

Results

Relation to dose of glucocorticoids used

Table 1 shows characteristics of patients classified by dose of glucocorticoids/day. The mean age was not different among three groups. Mean serum IgE levels were lowest in group A, patients treated with 5 mg of prednisolone or more for 2 years or more, however no significant difference was present in serum IgE levels among three groups. Figure 1 shows proportion of each clinical type of asthma in the three asthma groups. The proportion of type Ia− 1 asthma was higher in group C, patients treated without glucocorticoids. In contrast, the proportion of

type II asthma higher in group A and group B, patients treated with prednisolone of 5 mg or less for less than 2 years, compared to that in group C.

Table 1. Characteristics of patients with asthma, classified by dose of glucocorticoids perday

Asthma group	No of patients	Age (years)	Serum IgE (IU/ml)
A	37	54.4	299 (18-3058)
B	25	53.5	590 (18-2420)
C	32	57.4	437 (11-1397)

A; patients treated with prednisolone of 5 mg/day or more for more than 2 years, B: patients treated with prednisolone of less than 5 mg/day for less than 2 years, C: patients treated without prednisolone.

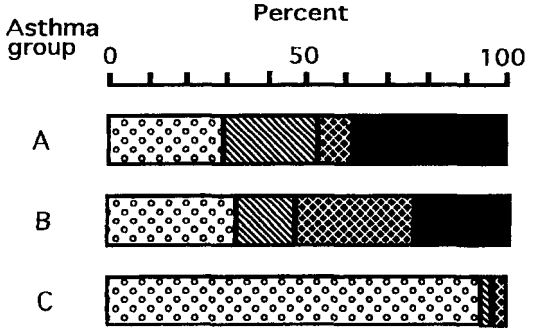

Fig. 1. Dose of glucocorticoids used and clinical asthma types in patients with asthma. Clinical asthma type : type Ia－1 ( ), Ia－2 ( ), Ib ( ), and II ( ). A : patients treated with prednisolone of 5 mg/day or more for more than 2 years, B : patients treated with prednisolone of less than 5 mg/day for less than 2 years, C : patients without prednisolone.

Serum cortisol level was significantly higher in group C (12.6 ± 3.9mcg/dl) than in group B (6.8 ± 3.7mcg/dl) ($p<0.001$) and than in group A (2.4 ± 1.2mcg/dl) ($p<0.001$). The level was significantly higher in group B compared to that in group A ($p<0.001$) (Fig. 2).

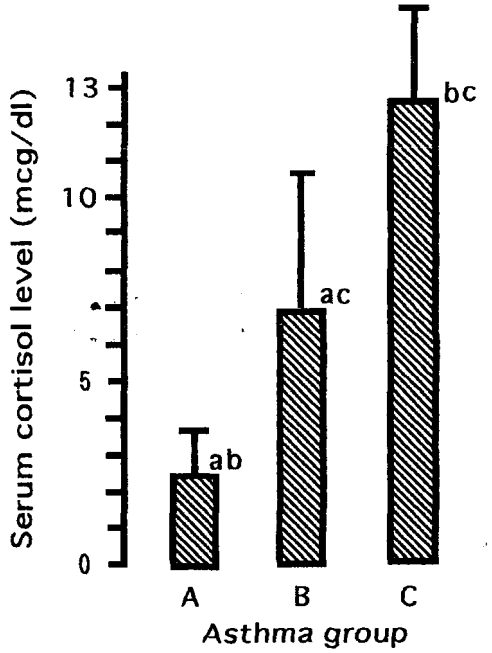

Fig. 2. Serum cortisol levels in each asthma group classified by glucocorticoids used. A : patients treated with prednisolone of 5 mg/day or more for more than 2 years, B : patients treated with prednisolone of less than 5 mg/day for less than 2 years, C : patients without prednisolone. a, b, and c ; $p<0.001$.

Relation to patient age

The serum cortisol level in patients of group C (patients treated without glucocorticoids) was significantly lower in patients over the age of 70 years (9.5 ± 3.6mcg/dl) compared to that in patients aged between 0 and 39 years (15.5 ± 2.0mcg/dl) ($p<0.01$), in those between 40 and 49 (15.6

± 2.5mcg／dℓ) ($p<0.05$), and in those between 50 and 59 (13.9 ± 3.0mcg／dℓ) ($p<0.02$) (Fig. 3).

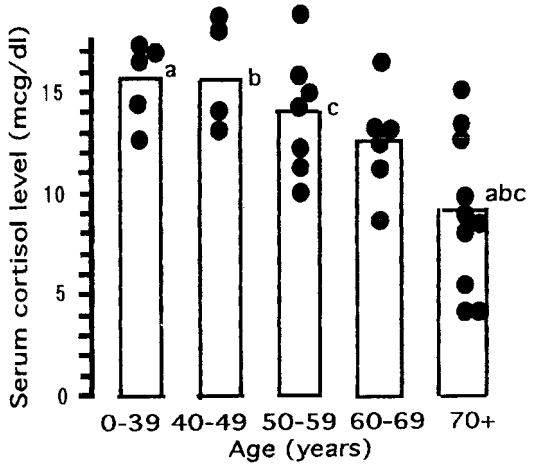

Fig. 3. Serum cortisol levels in asthma patients of group C (treated without prednisolone), classified by age. a, $p<0.01$, b ; $p<0.05$, c ; $p<0.02$.

The level of serum cortisol in patients of group B (patients treated with prednisolone of 5 ㎎ or less for less than 2 years) was lowest in patients aged between 50 and 59 years (5.8 ± 3.4mcg／dℓ), however, there were no significant differences among five age groups (Fig. 4).

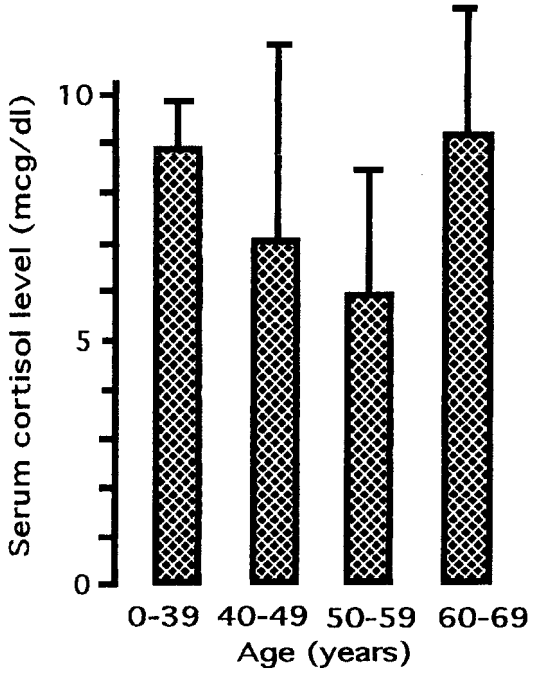

Fig. 4. Serum cortisol levels in asthma patients of group B (treated with prednisolone of less than 5 ㎎／day for less than 2 years), classified by age.

In group A patients (treated with prednisolone of 5 ㎎ or more for more than 2 years), the serum cortisol level was in general low (range 1.8－2.8mcg／dℓ), although no significant differences were present among five age groups (Fig. 5).

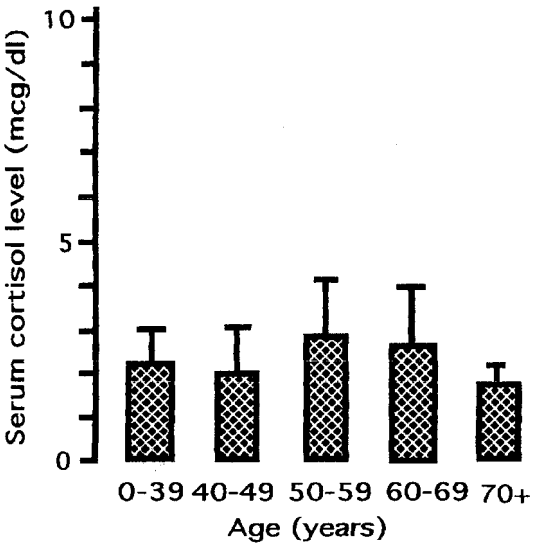

Fig. 5. Serum cortisol levels in asthma patients of group A (treated with prednisolone of 5 mg/day or more for more than 2 years), classified by age.

Discussion

In recent years, airways inflammation has been noted as one of the main onset mechanisms of asthma attacks, relating to severity and chronicity of attacks in adult patients[9]. Airway inflammation is also related to pathophysiological changes in the airways[16], and closely to clinical types of asthma[14, 15]. In analysis of bronchoalveolar lavage (BAL) cells, it has been clarified that BAL neutrophilia is closely correlated to type II bronchiolar obstructive asthma, and BAL eosinophilia to type Ib hypersecretion asthma[15]. Regarding correlation between clinical asthma types and dose of glucocorticoids used per day, the proportion of type Ia－1 (simple bronchoconstriction type) was highest in group C patients (treated without glucocorticoids). In contrast, the proportion of type II (bronchiolar obstruction type) was often observed in group A asthma patients (treated with glucocorticoids for more than 2 years).

Long-term glucocorticoid therapy suppresses the function of the adrenocortical glands, leading to decreased levels of serum cortisol[10, 11]. The level of serum cortisol was significantly lower in group A compared to that in group B and C. The results demonstrate that patients with group A including high proportion of type II asthma require larger dose of glucocorticoids, and in these patients, serum cortisol level was lower compared to group B and C.

In group C patients (treated without glucocorticoids), the level of serum cortisol was significantly lower in patients over the age of 70 years compared to that in those aged between 0 and 39 years, and between 40 and 49. The level in patients aged between 60 and 69 years was also low compared to that in those between 0 and 39, however, this was not significant. The results suggest that the level of serum cortisol decreases with aging.

References

1. Ishizaka T, Ishizaka K, Conrad DH, Froese A : A new concept of mechanism of IgE-mediated histamine release. J Allergy Clin Immunol 64 : 320－330, 1978.
2. 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.
3. Tanizaki Y, Sudo M, Kitani H, Araki H, Oki K, Tsuji M, Takahashi K, Kimura I : Eosinophilic leukocytes and arylsulphatase activity in bronchoalveolar lavage fluid of patients with bronchial asthma. Acta Med Okayama 42 : 227－230, 1986.

4. Gonzalez MC, Diaz P, Galleguillos FR, Ancic P, Cromwell O, Kay AB : Allergen induced recruitment of bronchoalveolar helper (OKT 4) and suppressor (OKT 8) T cells in asthma. Am Rev Respir Dis 136 : 600−604, 1985.

5. Durham SR : The significance of late response in asthma. Clin Exp Allergy 21 : 3 − 7, 1991.

6. Kirby JG, Hargreave FE, Gleich GJ, O'Byrne PM : Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. Am Rev Respir Dis 136 : 379−383, 1987.

7. Pauwels R : The relationship between airway inflammation and bronchial hyperresponsiveness. Clin Exp Allergy 19 : 395−398, 1989.

8. Kelly CA, Astenton SC, Ward G, Hendrick DJ, Walters EH : Lymphocyte subsets in bronchoalveolar lavage fluid obtained from stable asthmatics, and their correlation with bronchial responsiveness. Clin Exp Allergy 19 : 169−175, 1989.

9. Walker C, Kaegi MK, Brawn P, Blaser K : Activated T cells and eosinophilia in bronchoalveolar lavages from subjects with asthma correlated with disease severity. J Allergy Clin Immunol 88 : 935−942, 1991.

10. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Honke N, Kimura I : Clinical effects of complex spa therapy on patients with steroid-dependent intractable asthma (SDIA). Jpn J Allergol 42 : 219−227, 1993.

11. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Kimura I : Effects of lomg-term glucocorticoid therapy on bronchoalveolar cells in adult patients with bronchial asthma. J Asthma 30 : 309−318, 1993.

12. Tanizaki Y, Kitani H, Mifune T, Mitsunobu F, Kajimoto K, Sugimoto K : Effects of glucocorticoids on humoral and cellular immunity and on airway inflammation in patients with steroid-dependent intractable asthma. J Asthma 30 : 485−492, 1993.

13. Tanizaki Y, Sudo M, Kitani H, Kawauchi K, Mifune T, Takeyama H, Tada S, Takahashi K, Kimura I : Characteristics of cell components in bronchoalveolar lavage fluid (BALF) in patients with bronchial asthma. Jpn J Allergol 39 : 75−83, 1990.

14. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Ochi K, Harada H : Cellular composition of fluid in the airways of patients with house dust sensitive asthma, classified by clinical symptoms. Internal Medicine 31 : 333−338, 1992.

15. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Okano T, Honke N, Kimura I : A new modified classification of bronchial asthma based on clinical symptoms. Internal Medicine 32 : 197−203, 1993.

16. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Honke N, Kimura I : Pathophysiological changes in the airways of asthma patients with aging. Jpn J Allergol 41 : 1380−1387, 1992.

気管支喘息患者の血清コーチゾール値について．副腎皮質ホルモン投与および年齢との関連

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気管支喘息94例を対象に，副腎皮質ホルモン投与および年齢との関連のもとに，血清コーチゾール値の変動を観察した。まず副腎皮質ホルモンの投与量および投与期間により以下の3群に分けて検討した。グループA：副腎皮質ホルモン，プレドニソロンに換算して1日5㎎以上を2年間以上にわたり使用している症例，グループB：プレドニソロン1日5㎎以下で2年間以内の使用症例，グループC：副腎皮質ホルモンを全く使用していない症例。その結果，グループAの血清コーチゾール値（2.4 ± 1.2mcg／dℓ）は，グループB（6.8 ± 3.7mcg／dℓ）（p 0.01）やC（12.6 ± 3.9 mcg／dℓ）（p 0.001）に比べ有意に低い値であった。2．グループCでは，70才以上の症例の血清コーチゾール値は，0－39才の症例（p 0.01），40－49才の症例（p 0.05），そして，50－59才の症例（p 0.02）に比べ有意に低い値であった。

これらの結果は，血清コーチゾール値は，副腎皮質ホルモンの投与量や投与期間以外にも、加齢による影響を受ける可能性を示唆している。

キーワード：血清コーチゾール，気管支喘息，臨床病型，副腎皮質ホルモン，加齢