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## Spa therapy and serum cortisol levels in patients with steroid-dependent intractable asthma (SDIA)

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**Abstract :** Serum cortisol levels before and after spa therapy were compared in 30 patients with steroid-dependent intractable asthma (SDIA) in relation to clinical asthma types. 1. The mean level of serum cortisol in patients with type Ia-1 asthma was  $2.0 \pm 0.7$  mcg/dl before spa therapy, and significantly increased to  $9.0 \pm 3.1$  mcg/dl ( $p < 0.001$ ). The serum cortisol level of patients with type Ia-2 also significantly increased from  $3.3 \pm 1.5$  mcg/dl before spa therapy to  $5.9 \pm 3.1$  mcg/dl after the therapy ( $p < 0.05$ ). 2. The level of serum cortisol in patients with type Ib increased from  $4.0 \pm 1.6$  mcg/dl to  $7.8 \pm 1.4$  mcg/dl after spa therapy ( $p < 0.001$ ). In contrast, the serum cortisol levels in patients with type II were not significantly different before ( $2.7 \pm 1.3$  mcg/dl) and after spa therapy ( $3.5 \pm 3.0$  mcg/dl). The results showed that an increase in the levels of serum cortisol by spa therapy was more clearly observed in patients with type Ia-1 asthma compared to that in type Ia-2 or type Ib, and that, in contrast, the serum cortisol levels in patients with type II asthma did not significantly increase by spa therapy, since their asthma attacks were always severe and chronic in spite of long-term glucocorticoid regimen.

**Key Words :** Serum cortisol level, SDIA, clinical asthma type, spa therapy.

### Introduction

Bronchial asthma is characterized by dyspnea with wheezing, which is due to bronchoconstriction, mucus hypersecretion and edema of mucous membrane. In addition to these pathophysiological changes in airways, bronchiolar obstruction is sometimes

observed in adult patients with asthma. Asthma is classified into three (or four) types by these pathophysiological changes of airways ; Ia-1, Ia-2 (simple bronchoconstriction), Ib (bronchoconstriction + hypersecretion) and II (bronchiolar obstruction)<sup>1-3)</sup>. A relationship between asthma severity and clinical asthma type has been

observed, demonstrating that patients with steroid-dependent intractable asthma (SDIA) are often observed in type Ib and type II asthma.

Our previous studies have shown that spa therapy improves suppressed function of adrenocortical glands in patients with asthma<sup>4, 5</sup>). The action of spa therapy on adrenocortical glands is very important in the treatment for SDIA, since function of adrenocortical glands in patients with SDIA is always suppressed by long-term glucocorticoid regimen.

In the present study, to clarify the spa effects on adrenocortical glands in each clinical asthma type, serum cortisol levels were compared in patients with SDIA before and after spa therapy.

#### Subjects and Methods

The subjects were 30 patients with steroid-dependent intractable asthma (SDIA) (19 females and 11 males, mean age 59.9 years, range 23–72 years). The subjects were divided into four groups; types Ia-1, Ia-2, Ib and II, according to previously reported criteria<sup>1-3</sup>). All patients were evaluated as having SDIA, since they had been treated with oral glucocorticoids 5–20 mg/day of prednisolone) and inhaled glucocorticoids (200–800 mcg/day of beclomethasone) for more than 2 years.

Asthma classification was performed according to the criteria modified from those previously described<sup>6, 7</sup>).

Type Ia, simple bronchoconstriction: Patients with symptoms such as wheezing and dyspnea which are mainly elicited by bronchoconstriction. In this study, we divided this type into two subtypes according to the amount of expectoration: 0–49 ml/day

(Type Ia-1) and 50–99 ml/day (Type Ia-2).

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 by bronchiolar obstruction.

All patients were admitted to our hospital and underwent complex spa therapy (swimming training in a hot spring pool + inhalation of iodine salt solution + fango therapy) for 1 to 3 months<sup>4, 8, 9</sup>). Swimming training was carried out in a hot spring pool for 30 min a day and 5 times a week<sup>10, 11</sup>). Inhalation of 1.0 ml of iodine salt solution (KI 134 mg/l and NaCl 14.664 g/l) was performed twice a day<sup>12</sup>). In fango therapy, fango taken from Ningyo pass heated to 70–80°C was packed with cloth (40–43°C). The back of patients was covered with the fango, and warmed for 30 min 5 times a week<sup>13</sup>).

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 and before discharge from our hospital.

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

Statistically significant differences of the mean were estimated by unpaired Student's *t*-test. A value of  $<0.05$  was regarded as significant.

#### Results

Table 1 shows the characteristics of patients with steroid-dependent intractable asthma (SDIA) studied here. The patient age widely ranged in type Ia-1 and Ia-2 asthma.

In contrast, the range of patient age was narrow in type Ib and type II asthma. The mean age showed a tendency to be higher from type Ia-1 to type II (Fig. 1).

Table 1. Characteristics of patients with steroid-dependent intractable asthma (SDIA) studied

Asthma type	No of patients	Age (years)	Serum IgE (IU/ml)
Ia-1	10	46.1 (23-62)	424 (48-3058)
Ia-2	10	49.6 (23-61)	346 (11-1049)
Ib	5	55.4 (41-69)	332 (18-969)
II	5	64.0 (56-72)	461 (33-1820)

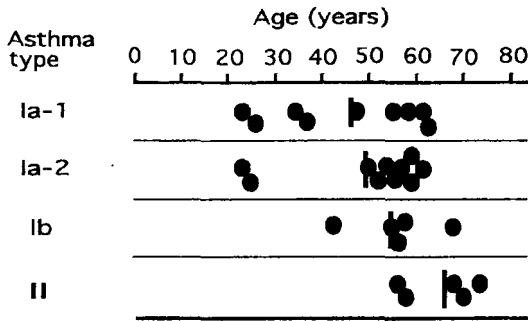


Fig. 1. Patient age in each clinical type of patients with steroid-dependent intractable asthma (SDIA)

The mean level of serum cortisol level in type Ia-1 asthma patients was  $2.0 \pm 0.7$  mcg/dl before spa therapy and  $9.0 \pm 3.1$  mcg/dl after the therapy. The level remarkably increased after the therapy and this difference was significant ( $p < 0.001$ ). The level of serum cortisol also significantly increased in the patients with type Ia-2 asthma from  $3.3 \pm 1.5$  mcg/dl to  $5.9 \pm 3.1$  mcg/dl ( $p < 0.05$ ). However, the increasing ratio was lower in type Ia-2 asthma

(+0.8) than in type Ia-1 (+3.5). The serum cortisol level in type Ib was significantly higher after spa therapy ( $7.8 \pm 1.4$  mcg/dl) compared to that before the therapy ( $4.0 \pm 1.6$  mcg/dl) ( $p < 0.001$ ), and the increasing ratio was +0.9. In contrast, the level of serum cortisol in type II asthma did not show significant increase after spa therapy ( $3.5 \pm 3.0$  mcg/dl) compared to that before the therapy ( $2.7 \pm 1.3$  mcg/dl), and the increasing ratio was +0.3. (Fig. 2).

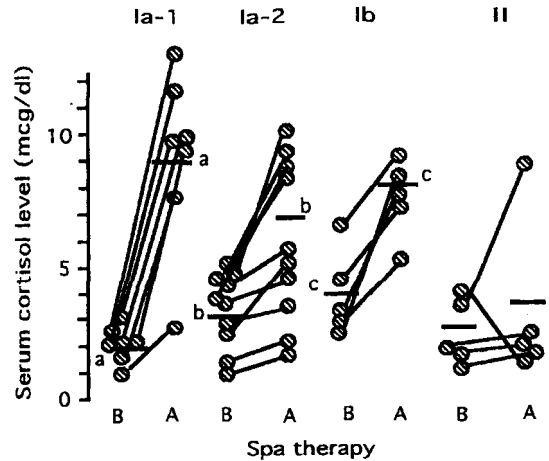


Fig. 2. Serum cortisol levels in each clinical asthma types of patients with steroid-dependent intractable asthma (SDIA) before (B) and after spa therapy (A). a and c;  $p < 0.001$ , b;  $p$ , 0.05.

### Discussion

The new concept that airway inflammation plays a major role in bronchial asthma<sup>14,15</sup>, even in mild asthma<sup>16,17</sup>, has been accepted in recent years. Furthermore, airway inflammation has been noted to correlated with severity of asthma attacks in adult patients. Our previous studies have clarified a correlation between airway inflammation and clinical asthma types by analysis of bronchoalveolar lavage (BAL) cells<sup>2, 3</sup>; BAL neutrophilia is

correlated to bronchiolar obstruction and BAL eosinophilia to hypersecretion. Our results also showed that an increase in number of neutrophils and/or eosinophils of BAL fluid often leads to steroid-dependent intractable asthma (SDIA). Therefore, in type Ia-2, Ib and II asthma patients, their attacks are often difficult to control with conventional antiasthma drugs.

Our previous studies have demonstrated that spa therapy improves symptoms<sup>4,7,18)</sup>, ventilatory function<sup>8)</sup> and condition of hypersecretion<sup>19)</sup>, and suppresses bronchial hyper-sensitivity<sup>20)</sup>. In addition to these spa effects, suppressed function of adrenocortical glands is improved by the therapy<sup>5)</sup>. In the present study, improvement of function of adrenocortical glands by spa therapy was compared among four clinical asthma types. The results showed that serum cortisol levels were more improved in patients with type Ia-1 asthma than in those with type II asthma after spa therapy. The levels of serum cortisol in patients with type Ia-2 and Ib asthma were also significantly increased after spa therapy. However, the increasing ratio in serum cortisol levels after spa therapy was different among four clinical asthma types. This difference may be due to dose of glucocorticoids used during their admission. To control attacks of patients with type II asthma, larger dose of glucocorticoids was required compared to those with other asthma types, and it was difficult to reduce the dose of glucocorticoids during their admission.

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## ステロイド依存性重症難治性気管支喘息患者の血清コルチゾールに対する温泉療法の影響

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簡潔表題：温泉療法と血清コルチゾール

索引用語：血清コルチゾール値, ステロイド依存性重症難治性気管支喘息, 気管支喘息臨床病型, 温泉療法

要旨：ステロイド依存性重症難治性気管支喘息患者30名において温泉療法前後の血清コルチゾール値を、臨床病型に基づいて検討した。

1. I a-1 型の症例における血清コルチゾール

値は温泉療法前の $2.0 \pm 0.7 \mu\text{g}/\text{dl}$ から $9.0 \pm 3.1 \mu\text{g}/\text{dl}$ に有意に増加していた ( $p < 0.001$ )。I a-2 型でも $3.3 \pm 1.5 \mu\text{g}/\text{dl}$ から $5.9 \pm 3.1 \mu\text{g}/\text{dl}$ に有意に増加していた ( $p < 0.05$ )。

2. I b型では温泉療法前後で $4.0 \pm 1.6 \mu\text{g}/\text{dl}$ から $7.8 \pm 1.4 \mu\text{g}/\text{dl}$ に有意に増加した。一方、II型の症例では、温泉療法前 $2.7 \pm 1.3 \mu\text{g}/\text{dl}$ 、温泉療法後 $3.5 \pm 3.0 \mu\text{g}/\text{dl}$ で有意な変化は認められなかった。

以上のように、温泉療法の血清コルチゾールに対する効果は、I a-2, Ib型に比較してI a-1型で明らかであった。一方、II型の気管支喘息症例の血清コルチゾール値は、温泉療法によって有意な変化を認めなかった。これは長期にわたる副腎皮質ホルモン投与にかかわらず、II型の症例の喘息発作は常に慢性的で重篤であるからと考えられる。