

ORIGINAL ARTICLE

Efficacy of inpatient treatment for atopic dermatitis evaluated by changes in serum cortisol levels

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ABSTRACT

When dealing with patients with severe atopic dermatitis (AD), inpatient treatment is useful for alleviating skin symptoms in short periods of time. We previously found that many severe AD patients had low serum cortisol levels at admission. The present study was undertaken to evaluate the efficacy of inpatient treatment in 29 adults with AD through comparisons of serum cortisol, plasma adrenocorticotrophic hormone (ACTH), serum thymus and activation-regulated chemokine (TARC), and serum lactate dehydrogenase (LDH) levels at admission with those at the time of discharge. Serum cortisol and plasma ACTH levels were significantly higher at discharge. On the other hand, serum TARC and serum LDH were significantly lower at discharge. We examined whether the suppression of hypothalamic–pituitary–adrenocortical function that was seen at admission was attributable to disturbed circadian rhythms due to sleep disorders by analyzing hypothalamic–pituitary–adrenocortical function in relation to the presence/absence of sleep disorders, serum cortisol levels and daily urinary free cortisol. Of the 17 patients with low serum cortisol levels upon admission, 15 (88.2%) had sleep disorders upon admission. However, the daily urinary free cortisol increased significantly from 8.0 ± 5.5 $\mu\text{g/day}$ (at admission) to 18.5 ± 17.2 $\mu\text{g/day}$ (at discharge). These results suggested that the suppression of endocrine function seen at admission was not attributable to disturbed circadian rhythms due to sleep disorders but represented true suppression of the endocrine system. These results indicated that inpatient care was useful for treating patients with severe AD, enabling efficient improvement of the skin condition and recovery from suppressed endocrine function.

Key words: atopic dermatitis, inpatient treatment, serum cortisol level, topical steroids, urinary free cortisol.

INTRODUCTION

When dealing with patients with severe atopic dermatitis (AD), short-term intensive inpatient treatment can alleviate skin symptoms rapidly, facilitating the early resumption of social activities by the patients. We previously reported that patients with acutely aggravating AD or severe AD that required hospitalization had low serum cortisol levels at admission and significantly higher serum cortisol levels at the time of discharge from the hospital.¹ The present study was undertaken to evaluate the efficacy of inpatient treatment in patients with severe AD through comparisons of serum cortisol, plasma adrenocorticotrophic hormone (ACTH), serum thymus and activation-regulated chemokine (TARC), and serum lactate dehydrogenase (LDH) levels at admission with those at the time of discharge from the hospital and through evaluations of severity classification of AD by the Japanese Dermatological Association (JDA) and visual analog scale (VAS) scores of itching sensation. Furthermore, in order to explore the mechanisms underlying the suppression of adrenocortical function that was seen at admission, adrenocortical function was analyzed in relation to the

presence/absence of sleep disorders, serum cortisol levels and the daily urinary free cortisol. The results from this study are presented and discussed in this paper.

METHODS

Patients

Twenty-nine adult AD patients (17 male and 12 female) who visited our hospital between November 2009 and June 2010 and who were aged 21–46 years (average, 32.6) were medicated for 8–15 days (average, 11.1) with inpatient treatment. The severity of AD upon admission was moderate (<10% of the body surface was covered by eruptions that were accompanied by intense inflammation) in eight patients, severe ($\geq 10\%$ and less than 30% of the body surface was covered by eruptions that were accompanied by intense inflammation) in 12 patients, and most severe ($\geq 30\%$ of the body surface was covered by eruptions that were accompanied by intense inflammation) in nine patients. The diagnosis of AD was made according to the criteria of the JDA.² Each patient provided a written consent for participating.

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Evaluation

Serum cortisol levels (reference value, 4.0–23.2 $\mu\text{g/dL}$), plasma ACTH levels (reference value, 7–56 pg/mL), serum TARC levels (reference value, <450 pg/mL) and serum LDH levels (reference value, 275–512 IU/L) were measured upon admission and at the time of discharge from the hospital. Blood was sampled between 07.00 and 08.00 hours on the second day after admission and on the day of discharge from the hospital. In addition, severity classification of AD by the JDA and VAS scores of itching sensations were evaluated.

Measures

Severity classification of AD by the JDA. For the severity classifications, three elements of eruption (erythema/acute papules, exudation/crusts, and chronic papules/nodules/lichenification: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe) were evaluated in the most severely affected part of each of five body regions (head/neck, anterior trunk, posterior trunk, upper limbs and lower limbs). The areas of eruption on the five body regions were also evaluated. Evaluation of the areas of eruption were done while considering all three elements (0 = no eruption, 1 = less than one-third, 2 = one-third to two-thirds, 3 = more than two-thirds). Both scores were added (maximum, 60 points).³

VAS scores of itch. Itch was assessed by the patients using a 0–100-mm scale, with the low extreme indicating a complete absence of the sensation and the high end indicating an extremely pronounced degree of the sensation. The patients themselves marked the scale, and the length from the left end was measured to determine the VAS scores.

Statistics

Paired Student's *t*-tests were used to compare the indices before and after inpatient treatment. Each value was presented as the mean $\pm$ standard deviation (SD). Plasma ACTH readings of less than 5 pg/mL were regarded as 5 pg/mL . The readings of daily urinary free cortisol of less than 5.5 $\mu\text{g/day}$ were regarded as 5.5 $\mu\text{g/day}$.

RESULTS

Serum cortisol levels were 4.6 ± 4.8 $\mu\text{g/dL}$ (mean $\pm$ SD) and 9.2 ± 4.1 $\mu\text{g/dL}$ before and after inpatient treatment, respectively (Fig. 1). There was a statistical difference in this value ($P = 0.0003$, paired Student's *t*-test). Plasma ACTH levels were 16.0 ± 14.3 and 25.2 ± 15.3 pg/mL before and after inpatient treatment, respectively (Fig. 2). There was a statistical difference in this value ($P = 0.0261$, paired Student's *t*-test). Serum TARC levels were 7486.2 ± 10201.2 and 1284.8 ± 1111.4 pg/mL before and after inpatient treatment, respectively (Fig. 3). There was a statistical difference in this value ($P = 0.0033$, paired Student's *t*-test). Serum LDH levels were 719.4 ± 287.5 and 466.2 ± 82.6 IU/L before and after inpatient treatment, respectively (Fig. 4). There was a statistical difference in this value ($P = 0.0002$, paired Student's *t*-test). The scores of the

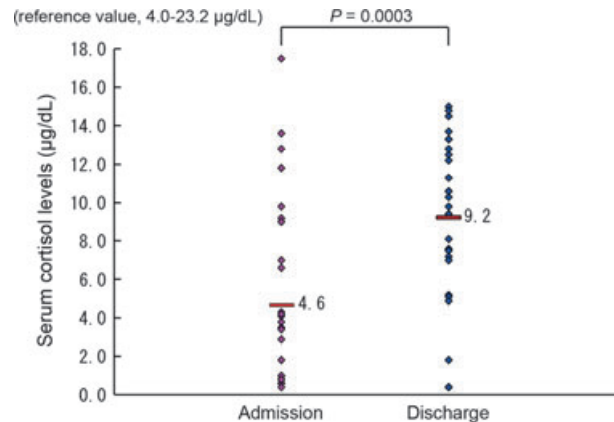


Figure 1. Comparison of serum cortisol levels before/after inpatient treatment.

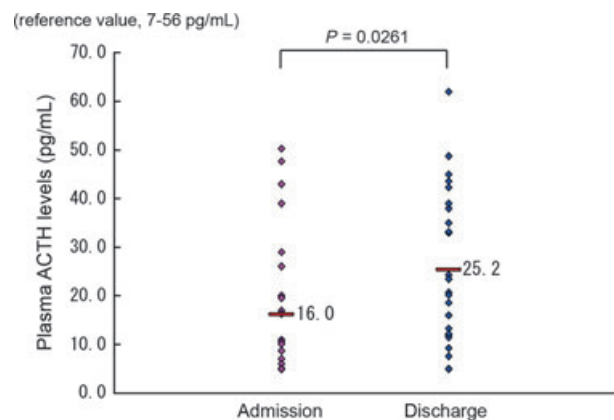


Figure 2. Comparison of plasma adrenocorticotrophic hormone (ACTH) levels before/after inpatient treatment.

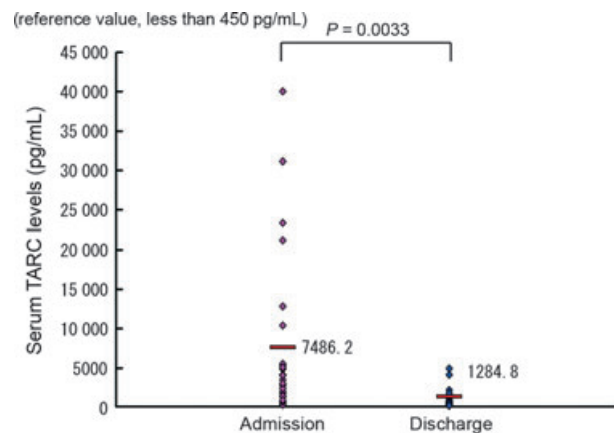


Figure 3. Comparison of serum thymus and activation-regulated chemokine (TARC) levels before/after inpatient treatment.

severity classification of AD by the JDA were 39.1 ± 9.5 and 14.2 ± 6.9 before and after inpatient treatment, respectively. There was a statistical difference in this value (paired Student's

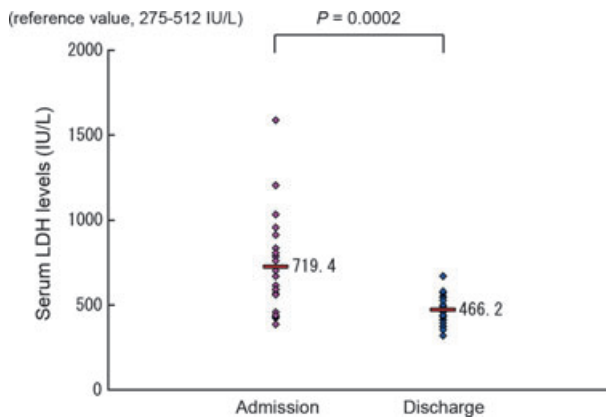


Figure 4. Comparison of serum lactate dehydrogenase (LDH) levels before/after inpatient treatment.

t-test, $P < 0.0001$). The VAS scores of Itch were 50.2 ± 22.8 and 10.5 ± 11.2 before and after inpatient treatment, respectively. There was a statistical difference in this value (paired Student's *t*-test, $P < 0.0001$).

DISCUSSION

Recently, the number of patients with AD has been increasing. The increase is particularly marked in the number of chronic and refractory severe cases requiring hospitalization. Inpatient treatment is quite important for acutely aggravating AD and severe/refractory AD from the viewpoint of early therapeutic intervention.⁴ Short-term intensive care by means of hospitalization facilitates the early resumption of social activities by the patients.

In our department, inpatient treatment, which primarily involves topical steroid therapy, has been actively applied to patients with acutely aggravating AD or severe/refractory AD. We previously reported that many patients with severe AD had low serum cortisol levels upon admission and higher serum cortisol levels at the time of discharge from the hospital.¹ The present study was undertaken to evaluate the efficacy of inpatient treatment in patients with severe AD through comparisons of serum cortisol, plasma ACTH, serum TARC and serum LDH levels at admission with those at the time of discharge from the hospital and through evaluations of severity classification of AD by the JDA and the VAS scores of itching sensation.

In all of the 29 inpatients studied, inpatient treatment (primarily by topical steroids) resulted in the alleviation of skin symptoms and statistically significant reductions of serum TARC levels, serum LDH levels, severity classification of AD by the JDA and VAS scores of itching sensation, and improvements in quality of life. Serum cortisol levels were less than $4.0 \mu\text{g/dL}$, indicating suppressed adrenocortical function, in 17 patients (58.6%) upon admission, but they returned to normal (significantly higher than the level upon admission) in 14 patients (82.3%) by the time of discharge from the hospital following inpatient treatment. In addition, plasma ACTH levels increased significantly following inpatient treatment. These results suggest that inpatient treatment of patients with severe

AD is a useful method of treatment that is expected not only to alleviate skin symptoms rapidly and efficiently, but also to facilitate recovery from suppressed endocrine (hypothalamic-pituitary-adrenocortical) function.

Low serum cortisol levels in patients with severe AD were described in 2007 by Haeck *et al.*⁵ Their study revealed significantly lower serum cortisol levels and significant increases in the prevalence of six area, six sign AD (SASSAD) and serum TARC levels in patients with severe AD compared to patients with mild AD. They additionally compared the data upon admission with the data at the time of discharge from the hospital in patients with severe AD and reported that serum cortisol levels at discharge were significantly higher than those at admission; moreover, significant reductions in the prevalence of SASSAD and serum TARC levels were noted. In the present study, serum cortisol levels at discharge were significantly higher than those at admission, and this was accompanied by significant reductions in severity classification of AD by the JDA and serum TARC levels, which were similar to the results reported by Haeck *et al.*⁵ Furthermore, serum LDH levels that are known to correlate with AD activity⁶ were significantly lower at the time of discharge than at admission.

Diseases known to present with compromised adrenocortical function include primary adrenal failure (Addison's disease), secondary adrenal failure (hypothalamic disorder and pituitary disorder) and steroid-induced dysfunction. Many reports have demonstrated that negative feedback following steroid treatment tended to reduce adrenocortical function in patients with AD.^{7,8} We previously evaluated patients with AD who received steroid withdrawal therapy (without using any topical steroids) before admission (no such case was included in the present study) and found that serum cortisol levels were markedly decreased in all of these patients at admission.¹ When these patients subsequently received topical steroid treatments, serum cortisol levels normalized in all of them by the time of discharge from the hospital.

Circadian rhythms are an important factor affecting adrenocortical function. It has been shown that sleep disorders or similar issues that are caused by intense nocturnal itch occasionally disturb circadian rhythms.⁹ In the present study of 29 patients, serum cortisol levels were low at admission in 17 patients, and 15 (88.2%) of these had sleep disorders at admission and were suspected of having disturbed circadian rhythms. Thus, we analyzed the presence/absence of sleep disorders and daily urinary free cortisol in 15 patients who were able to undergo daily urinary free cortisol excretion measurements among the 17 patients who showed low serum cortisol levels at admission in order to examine whether adrenocortical function was suppressed in these patients (Fig. 5). The daily urinary free cortisol (reference value, $11.2\text{--}80.3 \mu\text{g/day}$) increased significantly from $8.0 \pm 5.5 \mu\text{g/day}$ (at admission) to $18.5 \pm 17.2 \mu\text{g/day}$ (at the time of discharge; $P = 0.0330$, paired Student's *t*-test).

As described above, the course of suppressed adrenocortical function after admission was similar in patients who received steroid withdrawal therapy before admission, suggesting that the negative feedback of the steroid used before

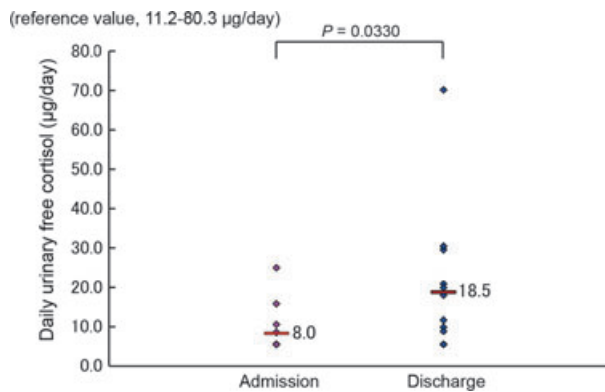


Figure 5. Comparison of daily urinary free cortisol levels before/after inpatient treatment.

admission was unlikely. Furthermore, these patients showed reductions in the daily urinary free cortisol levels, indicating that they did not show disturbed circadian rhythm, but truly suppressed adrenocortical function. At present, there is no definite answer to the question of whether the severe course of AD resulted in reductions of serum cortisol levels or whether the reduction of serum cortisol levels resulted in the severe course of AD, but there seems to be an association between the severe course of AD and the suppression of adrenocortical function. It has recently been reported that a skin stress response system (SSRS), which is equivalent to the hypothalamic-pituitary-adrenal axis functions, is induced when the skin is exposed to local stress.¹⁰ In this system, corticotropin-releasing hormone (CRH) and pro-opiomelanocortin-related peptides, which are produced in the hypothalamus and pituitary and act on systemic organs through blood circulation, are also produced in various peripheral tissues (including skin) when exposed to local stress. Therefore, when the skin is in conditions that are susceptible to irritation (e.g. in the presence of AD), it seems likely that local stress triggers the SSRS, possibly resulting in reductions of serum cortisol levels due to negative feedback by locally produced CRH. We plan to study the relationship of these factors in the near future (Fig. 6). It has been reported that during the course of wound healing after tissue injury, cortisol is synthesized in keratinocytes *in vitro* and in the epidermis *in vivo*. It has been speculated that such cortisol synthesis occurs for the purpose of limiting initial pro-inflammatory responses.¹¹ Tissue injury can also occur in patients with AD because of scratching or similar and it seems likely that cortisol is synthesized in the injured skin of patients with AD, possibly suppressing hypothalamic-pituitary-adrenal axis functions through negative feedback mechanism. In addition, according to some reports, in patients with psoriasis, daily mental stress correlates positively with aggravation of the symptoms of psoriasis and correlates negatively with serum cortisol level. It has additionally been shown that serum cortisol level is lower in patients who experience higher levels of stress on a day-to-day basis than in patients who experience less stress.¹²⁻¹⁴ To correlate with this, we will also analyze the relation of serum cortisol level with stress in patients with AD.

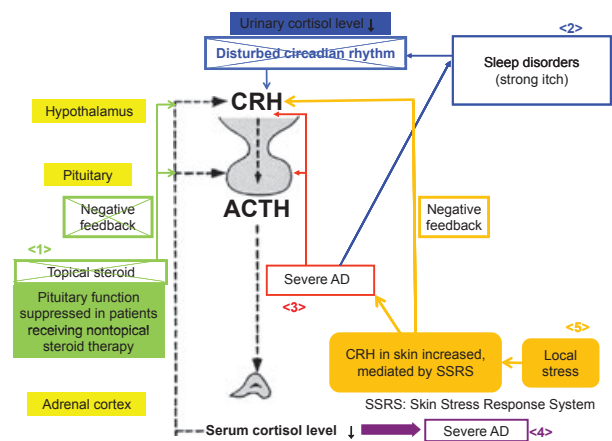


Figure 6. Relationship between severe atopic dermatitis (AD) and suppression of adrenocortical function. ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; SSRS, skin stress response system.

In the present study, topical steroids were primarily used for inpatient treatment. The topical steroid preparation used was an antidrug with a low incidence of systemic adverse reactions. Its dose level was 9.4 ± 5.7 g/day for the very strong class, 2.0 ± 3.4 g/day for the strong class and 11.4 ± 6.3 g/day in total. In all cases, this drug therapy was combined with azulene ointment or zinc oxide ointment plaster therapy. In all cases, topical steroid dose levels after admission were increased from the preadmission level or a type of steroid that was ranked in a higher place in terms of efficacy was used after admission. In 14 of these 17 cases (82.4%) showing lower than normal serum cortisol levels upon admission, serum cortisol levels returned to normal following such treatments. Of the 12 patients in whom the serum cortisol levels at admission were within the normal range, four patients (33.3%) showed reductions in serum cortisol levels following inpatient treatment, although the change in all of these cases was within the reference value.

In patients with AD presenting with suppressed adrenocortical function, adverse reactions to steroids (e.g. from abuse of topical steroids, oral steroid treatments) have conventionally been emphasized as factors that are possibly involved in such dysfunction. However, as shown in the present study, the adrenocortical function of patients with severe AD was occasionally suppressed without any relation to the negative feedback of steroids. Therefore, while care is needed to avoid the abuse of topical steroids or oral steroid preparations, therapeutic interventions with appropriate and sufficient topical steroids need to be applied positively when dealing with severe AD that requires hospitalization. Thus, the present study endorsed the efficacy of such an approach.

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