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Low basal serum cortisol in patients with severe atopic dermatitis: potent topical corticosteroids wrongfully accused

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Key words
atopic dermatitis, hypothalamus–pituitary–adrenal axis, serum cortisol levels, topical corticosteroids

Conflicts of interest
None declared.

Summary

Background Topical corticosteroids are used extensively to treat inflammatory skin disorders including atopic dermatitis (AD). Several studies have described temporary reversible suppression of hypothalamic–pituitary–adrenal function. However, sound evidence of permanent disturbance of adrenal gland function is lacking.

Objectives To relate basal cortisol levels to prior use of topical corticosteroids and disease activity in patients with moderate to severe AD and to investigate the effect on basal serum cortisol levels of topical corticosteroid treatment during hospitalization.

Methods Two groups of patients with AD were evaluated: 25 inpatients with severe AD who required hospitalization (group 1) and 28 outpatients with moderate to severe AD (group 2). In group 1, morning basal serum cortisol levels were measured twice, at admission and at discharge; in group 2, morning basal serum cortisol levels were measured once. Use of topical corticosteroids in the 3 months prior to the cortisol measurement was recorded and disease activity was monitored using the Six Area, Six Sign Atopic Dermatitis (SASSAD) score and serum thymus and activation-regulated chemokine (TARC) levels.

Results On admission, basal cortisol levels in group 1 were significantly (P < 0.001) decreased in 80% of the patients. In group 2, the basal cortisol levels were normal in all but three patients. Comparing the two groups, group 1 on admission had a significantly lower cortisol level than that of group 2 (P < 0.001). Disease activity in group 1 on admission was significantly higher than that of group 2 (P < 0.001). There was no difference in use of topical corticosteroids in the 3 months before cortisol measurement. At discharge in group 1 there was a significant increase (P < 0.0001) of basal cortisol levels and a significant (P < 0.001) decrease in disease activity reflected by the decrease in serum TARC levels and SASSAD score.

Conclusions Disease activity, rather than the use of topical corticosteroids, is responsible for the low basal cortisol values in patients with severe AD.

For many decades topical corticosteroids have been widely used to treat inflammatory skin disorders including atopic dermatitis (AD). Although dermatologists and general practitioners often prescribe topical corticosteroids, there is widespread concern about possible systemic side-effects, such as depression of adrenal gland function, osteoporosis, growth impairment in children, glaucoma and cataract. Corticophobia (fear of topical corticosteroid use) by patients and doctors often results in inadequate disease control in patients with inflammatory skin disorders.

The original active topical glucocorticoid is hydrocortisone, the natural glucocorticosteroid of the adrenal cortex. Shortly after its introduction as a treatment for inflammatory skin diseases, Malkinson and Ferguson found experimental evidence that some percutaneous absorption of hydrocortisone may occur. However, several years later, Fleischmajer found...
no evidence of systemic effects after application of large amounts of hydrocortisone in 19 patients with AD (age 5–60 years). In children with AD, percutaneous absorption of hydrocortisone was proven to be significantly lower in the convalescent phase of the disease compared with the acute phase, probably owing to the restoration of the skin barrier.4

Several years after the introduction of hydrocortisone, new synthetic corticosteroids were developed. Synthetic corticosteroids can modulate endogenous cortisol secretion by influencing hypothalamic and pituitary effects on adrenal gland activities through the hypothalamic–pituitary–adrenal (HPA) axis.5 The presence of synthetic corticosteroids in the circulation exerts a negative feedback on the release of hypothalamic corticotropin-releasing hormone (CRH). Diminished CRH release results in a decrease in corticotropin (ACTH) release from the pituitary gland, which in turn leads to decreased production of endogenous cortisol by the adrenal gland.

As early as 1965, Scoggins and Kliman6 concluded that the cortisol content of plasma in the early morning proved to be a very sensitive index of the suppression of pituitary–adrenal function by synthetic corticosteroid analogues. Nowadays, measuring total basal serum cortisol (between 08.00 and 09.00 h) is still the most commonly used method for the initial evaluation of adrenal gland function. Although there is convincing evidence that percutaneous absorption of topical corticosteroids can occur, especially using potent topical corticosteroids on large areas of inflamed skin and for longer periods, the question remains whether this is relevant in clinical practice. Several studies and case reports describe temporary reversible suppression of HPA function,5,7 but there is no circumstantial evidence of permanent disturbance of adrenal gland function. When treating patients with severe AD it is important to estimate the risk–benefit ratio when using potent topical corticosteroids, because the alternative treatment options in this patient group, such as oral immunosuppressive drugs, also have side-effects when used for extended periods.

The aim of the current study was to investigate basal serum cortisol levels of adult patients with moderate to severe AD in relation to the total amount of topical corticosteroid used in the past 3 months and to the disease activity. In addition, the effect was investigated of intensive topical corticosteroid treatment on basal serum cortisol level and disease activity in patients with severe AD during admission to hospital.

Patients and methods

Patients

Fifty-three patients with moderate to severe AD were studied. The inpatients (group 1) consisted of 25 patients (11 men and 14 women, age range 18–83 years; mean age 39) with severe uncontrolled AD that required hospitalization. Twenty-eight outpatients (12 men and 16 women, age range 18–74 years; mean age 36) with moderate to severe but controlled AD served as a control group (group 2). The diagnosis of AD was made according to the criteria of Hanifin and Rajka.8 None of the patients were pregnant at inclusion. Menopausal state (including use of oestrogen replacement therapy), use of oral contraception, use of antidepressants, mean intake of alcohol per week, height and weight were recorded on inclusion. The potency of topical corticosteroids used was rated as class 1, 2, 3 or 4; class 1 is the least potent and class 4 is the most potent. Both groups used topical corticosteroids of class 2, 3 or 4 prior to evaluation. The local medical ethical committee approved this study.

Basal cortisol levels

Basal serum cortisol levels were determined between 08.00 and 09.00 h in group 1 (on first day of admission) and group 2 using the automated immunoanalyser Advia Centaur (Bayer HealthCare, Mijdrecht, the Netherlands). Total imprecision over the range 0·1–0·9 μmol L–1 was 7·5–10%. In group 1, measurement of the basal cortisol level was repeated on the morning of discharge. To be sure that we solely measured endogenous cortisol levels in the assay used, we tested the cross-reactivity of the various corticosteroids administered with the assay used.

Disease activity

In group 1, disease activity was recorded on the first day of admission and on the day of discharge using the Six Area, Six Sign Atopic Dermatitis (SASSAD) score9 and by determining the level of serum thymus and activation-regulated chemokine (TARC/CCL17).10–12 In group 2, the disease activity was also recorded (on a visit to the outpatient clinic) using the SASSAD score and by measuring the level of TARC in peripheral blood.

Topical corticosteroid use

In both groups, the use of topical, inhaled and systemic corticosteroids was evaluated for the period of 3 months prior to admission or visit to the outpatient clinic. This was carried out using a combination of the patient’s history and pharmacy records obtained. We strove as accurately as possible to quantify the exact amount of topical corticosteroid used. Using this method, we anticipate that there is an overestimation of the actual use of topical corticosteroids as not all patients use the topical steroids they obtain from the pharmacy and/or accurately estimate their use. The topical corticosteroid use is expressed as the total amount (in g) used over the 3 months prior to measurement of basal cortisol levels. During admission (group 1), we did not impose a previously specified treatment regimen and patients were treated as they would have been otherwise. We subsequently recorded this treatment modality.

Statistical analysis

Statistical analysis was performed using the program SPSS for Windows (version 12, 2003; SPSS Inc., Chicago, Ill., U.S.A.).

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Because clearly skewed distributions in outcome parameters were observed, nonparametric tests were used. Associations between variables were tested in contingency tables using Fisher’s exact test or the χ² test (with Yates’ continuity correction). Differences in median values between independent variables were tested using the Mann–Whitney test or the Kruskal–Wallis test (corrected for tied values). The Spearman rank correlation test was used to measure correlations between variables. Probability levels of 0.05 and below were considered significant.

**Results**

**Group 1 (admission) vs. group 2**

**Basal cortisol levels**

The clinical characteristics of the patients are summarized in Table 1. Basal cortisol levels on admission in the inpatients (group 1) were significantly (P < 0.001) decreased in 20 of the 25 patients (80%), including six of seven patients using oral contraceptives. Mean cortisol levels at admission were 0.087 μmol L⁻¹ lower than the lower limit of the reference range for cortisol (0.20 μmol L⁻¹) [95% confidence interval (CI) of difference 0.018–0.157] (P < 0.05). In the outpatients (group 2), basal cortisol levels were normal (> 0.20 μmol L⁻¹) in all but three patients.

Comparing the two groups, the basal cortisol levels of group 1 patients at admission were significantly lower than those of group 2 (P < 0.001). The mean ± SD difference between the mean basal cortisol levels of group 1 (at admission) and group 2 is 0.374 ± 0.06 μmol L⁻¹ (95% CI of difference 0.254–0.494) (Fig. 1a). This difference is also significant when correcting for use of oral contraceptives.

Testing the assay, the basal cortisol levels measured were not influenced by the addition of the various synthetic corticosteroids and it can be concluded that there is no cross-reactivity in this assay.

**Disease activity**

Disease activity in group 1 on admission was significantly (P < 0.001) higher than the disease activity in group 2 as indicated by a higher level of TARC in group 1 with a mean ± SD of 5037 ± 5841 pg mL⁻¹ (95% CI 2511–7563) vs. a mean ± SD in group 2 of 1391 ± 2005 pg mL⁻¹ (95% CI 581–2201) (Fig. 1b) and by a significantly (P < 0.001) higher mean ± SD SASSAD score in group 1 of 41 ± 16 (95% CI 33–49) vs. a score in group 2 of 19 ± 8 (95% CI 15–22).

**Topical corticosteroid use**

There was no significant difference in the amount of topical corticosteroids used between the two groups in the 3 months.
prior to basal cortisol measurement. Group 1 had used $339 \pm 151$ g (mean $\pm$ SD) in 3 months and group 2 had used $326 \pm 258$ g (mean $\pm$ SD) of topical corticosteroids in 3 months ($P = 0.8$), with a mean difference of $12$ g [SEM 60:2 and 95% CI $(−133)$–109]. There was no significant difference between group 1 and 2 in potency of topical corticosteroids used ($P = 0.963$), use of inhaled corticosteroids ($P = 1$) and use of oral corticosteroids in the 3 months prior to inclusion ($P = 0.365$) (Table 2).

**Within-group comparison**

No significant correlation was found between the basal cortisol levels and use of topical corticosteroids in groups 1 and 2 ($P = 0.287$ and $P = 0.181$, respectively; Spearman rank correlation test). In addition, there was no association between the basal cortisol levels and the potency of topical corticosteroids used ($P = 0.787$ for group 1 and $P = 0.182$ for group 2; Kruskal–Wallis test), use of inhaled corticosteroids ($P = 0.514$ for group 1 and $P = 0.418$ for group 2; Mann–Whitney test) and use of oral corticosteroids ($P = 0.329$ for group 1 and $P = 0.634$ for group 2; Mann–Whitney test). Furthermore, there was no significant difference in body mass index, number of patients using antidepressants, alcohol intake per week, number of postmenopausal women and number of women using contraceptives between the two groups (Table 1).

**Group 1: effect of hospitalization**

In group 1 there was a significant increase during treatment in hospital ($P < 0.0001$) of basal cortisol levels in comparison with the admission values, with a mean increase of $0.39$ mmol L$^{-1}$ (95% CI 0.26–0.52) (Fig. 2a). This increase was less but still significant ($P < 0.001$) when correcting for oral contraceptive use, with a mean increase of $0.26$ mmol L$^{-1}$ (95% CI 0.16–0.37). At discharge, the serum TARC levels had significantly ($P < 0.001$) decreased in comparison with admission, with a mean decrease of 2900 pg mL$^{-1}$ (95% CI 1542–4261) (Fig. 2b). The mean $\pm$ SD SASSAD score of this group on admission was $41 \pm 16$ and at discharge the SASSAD score had decreased significantly to $9 \pm 5$ ($P < 0.001$). There was no difference in effect between the different treatment modalities used during hospitalization in group 1 on the rise in basal cortisol levels (Table 3). At discharge in group 1 there were four patients who still had basal cortisol levels below the lower limit of the reference range ($0.20$ mmol L$^{-1}$); however, 6 weeks after discharge they too increased to normal levels.

**Group 1 (discharge) vs. group 2**

Comparing the two groups again, this time comparing group 1 at discharge with group 2, neither the mean basal cortisol levels nor the serum TARC levels differed significantly ($P = 0.846$ and $P = 0.409$). The difference in cortisol was also not significant when correcting for use of oral contraceptives. The difference in the mean basal cortisol level at discharge in group 1 (mean $\pm$ SD $0.50 \pm 0.31$ mmol L$^{-1}$) and group 2 (mean $\pm$ SD $0.49 \pm 0.25$ mmol L$^{-1}$) is $0.015$ mmol L$^{-1}$ [SEM $0.077$ mmol L$^{-1}$, 95% CI $(−0.14)$–0.17] and the difference in

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**Table 2** Comparison of the inpatient group and outpatient group in use of topical, inhaled and oral corticosteroids and potency of topical corticosteroids used

<table>
<thead>
<tr>
<th>Steroid use in 3 months prior to cortisol measurement</th>
<th>Group 1 vs. group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean amount of topical corticosteroids in g</td>
<td>$P = 0.8$</td>
</tr>
<tr>
<td>Inhaled corticosteroids (yes/no)</td>
<td>$P = 1$</td>
</tr>
<tr>
<td>Oral corticosteroids (yes/no)</td>
<td>$P = 0.365$</td>
</tr>
<tr>
<td>Potency of topical corticosteroids (class 2–4)</td>
<td>$P = 0.963$</td>
</tr>
</tbody>
</table>

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mean TARC level is 699 pg mL⁻¹ [SEM 836 pg mL⁻¹, 95% CI (−998)–2396].

**Discussion**

In this prospective, parallel cohort study we have demonstrated that low basal serum cortisol values are not caused by prior use of potent topical corticosteroids in patients with moderate to severe AD. Within both the inpatient and outpatient groups, no significant correlation was found between the amount of topical corticosteroids used and basal serum cortisol values. Furthermore, in the inpatient group (group 1) with active disease, significantly lower basal serum cortisol levels were found compared with the outpatient group (group 2) with controlled disease, whereas there was no significant difference in topical corticosteroid use in both groups. Notably, basal serum cortisol levels of the inpatients showed a dramatic increase during intensive treatment with large amounts of potent topical corticosteroids.

The results of our study invalidate overall opinion that treatment with potent topical corticosteroids suppresses function of the HPA axis. In the past, many studies have been performed linking the use of topical corticosteroids to HPA axis dysfunction, with contradictory results. Although there seems to be laboratory evidence of reversible suppression of the HPA axis in patients treated with topical corticosteroids, irreversible adrenal insufficiency is found only in rare cases.¹³ One of the limitations of most studies is that they were not primarily designed to study HPA axis function. Most studies show retrospective data and no information is given on disease severity at the moment of testing nor on the amount of topical corticosteroids used before testing. Although this study was designed primarily to relate topical corticosteroid use and disease activity to basal serum cortisol levels, its limitation probably lies in the difficulty of exactly quantifying the amount of topical corticosteroids used by patients in the weeks prior to measurement of basal serum cortisol level. Weighing the corticosteroid tubes was attempted but was very inaccurate as

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**Table 3** Treatment group 1 during hospitalization in relation to basal cortisol levels

<table>
<thead>
<tr>
<th>Treatment during hospitalization</th>
<th>Number of patients (n = 25)</th>
<th>Basal cortisol levels (µmol L⁻¹)</th>
<th>Admission</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>13</td>
<td>0·10 ± 0·16ᵃ</td>
<td>0·44 ± 0·29ᵃ</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids under occlusion</td>
<td>2</td>
<td>&lt; 0·01</td>
<td>0·12</td>
<td></td>
</tr>
<tr>
<td>Tar preparations</td>
<td>3</td>
<td>0·04</td>
<td>1·13</td>
<td></td>
</tr>
<tr>
<td>Tar preparations and topical corticosteroids</td>
<td>2</td>
<td>0·1</td>
<td>0·30</td>
<td></td>
</tr>
<tr>
<td>Oral immunosuppressants and topical corticosteroids</td>
<td>3</td>
<td>0·18</td>
<td>1·11</td>
<td></td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>3</td>
<td>0·59</td>
<td>0·73</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>1</td>
<td>0·07</td>
<td>0·81</td>
<td></td>
</tr>
<tr>
<td>Prednisone and azathioprine</td>
<td>1</td>
<td>0·39</td>
<td>0·36</td>
<td></td>
</tr>
</tbody>
</table>

ᵃMean ± SD.
patients forgot their tubes and often did not know what they had received from the pharmacy. Using the pharmacy records in combination with the patient’s history, there was probably an overestimation of the actual use of topical corticosteroids. If this maximal amount of topical corticosteroids has no effect on the basal cortisol level, it is safe to reason that the actual amount used by patients certainly has no effect.

Several safety studies concerning the HPA axis were performed after the introduction of a potent topical corticosteroid, clobetasol-17-propionate. Olsen and Cornell14 demonstrated that clobetasol-17-propionate could induce a dose-related depression of cortisol level in hospitalized patients, with recovery of cortisol levels within 2 or 3 days after discontinuation. By contrast, Jegasothy et al.15 found serum cortisol levels below the normal limit in only seven of 113 outpatients with AD or psoriasis who were treated with clobetasol ointment two or three times daily (up to 50 g weekly) on two consecutive weeks. Cushing syndrome caused by the use of large amounts of clobetasol propionate 0.05% ointment during long treatment periods was described in two cases.16 Because patients did not regularly visit a doctor, there was an inappropriate use or abuse of this potent topical steroid in both cases. In an efficacy study, using fluticasone propionate ointment in adult patients with moderate to severe AD, van der Meer et al.17 also evaluated basal serum cortisol levels in a subgroup of patients for a longer period. No significant changes in basal serum cortisol were detected during the induction phase of 4 weeks (intensive topical corticosteroid use, n = 79), nor in the controlled maintenance phase of 16 weeks (topical corticosteroid use twice weekly, n = 13).

Children are believed to be especially at risk for systemic effects of topical corticosteroids, because of their relatively large body surface. Patel et al.18 studied the adrenal function in 14 prepubertal children with moderate to severe AD (age 3–10 years). No difference was found in basal serum cortisol levels between children with moderate to severe AD regularly treated with topical corticosteroids compared with controls. In a more recent open-label safety study on the effect of fluticasone propionate cream 0.05% twice daily over 3–4 weeks in 51 children with moderate to severe AD, no effect on basal serum cortisol levels was seen.19

Evidence that factors other than topical corticosteroid use are responsible for aberrant HPA axis activity in patients with AD comes from a study of Matsuda et al.,20 in which children with AD (age 2–18 years) who did not use topical corticosteroids before evaluation were compared with children who had routinely used topical corticosteroids. Although no significant difference in basal serum cortisol was found between the two groups, basal cortisol levels and the response to ACTH of the total AD group were significantly lower compared with controls.

If low basal serum cortisol is not linked to prior use of topical corticosteroids, what can be the reason for this observation? Matsuda et al. demonstrated that topical corticosteroid treatment during hospitalization in a group of children with AD who had not previously been treated with topical corticosteroids resulted in a significant decrease in disease activity that was paralleled by a significant increase in basal serum cortisol. These findings are in accordance with our own results showing that the significant decrease in disease activity after intensive treatment with large amounts of potent topical corticosteroids during the hospitalization period resulted in a considerable increase (normalization) in basal serum cortisol levels. It would appear that HPA axis function is influenced more by disease activity than by systemic effects of potent topical corticosteroids. This hypothesis is further supported by the fact that the patients with severe and extensive disease who needed hospitalization (inpatient group) used as little as 30 g topical corticosteroids weekly before their admission, whereas their basal serum cortisol was below the lower limit of the reference range for cortisol in 80% of the patients. During hospitalization, when potent topical corticosteroids were applied by dermatological nurses, approximately 25 g twice daily was used during the first week (approximately 350 g weekly) in the acute phase and once daily in the convalescent phase (approximately 150–175 g weekly). Despite the fact that some percutaneous absorption must have taken place, morning serum cortisol levels increased. The data from our study and those of Matsuda et al. suggest that disease activity is linked to low basal serum cortisol levels. This is of special interest because appropriate reactivity of the HPA axis to stressful stimuli, such as inflammation, may be necessary to control immunological processes. During inflammatory processes, the release of proinflammatory cytokines, such as interleukin (IL)-1β, tumour necrosis factor-α and IL-6, stimulates the HPA axis to produce larger amounts of glucocorticoids.21,22 The increased adrenal glucocorticoid production can suppress inflammatory responses, thus preventing chronicity. Data from animal studies also suggest that the HPA axis might play a protective role in chronic inflammation.23

Interestingly, attenuated responsiveness of the HPA axis in adults and children with AD who were corticosteroid free for at least 3 months was found by Buske-Kirschbaum et al.24,25 Significantly attenuated cortisol and ACTH responses to a standardized laboratory psychological stressor were found in AD patients compared with nonatopic controls, whereas basal serum cortisol levels were comparable. The possible existence of a defective HPA axis has been studied extensively in rheumatoid arthritis (RA). Several small studies indicate a possible inability to mount adequate cortisol responses to inflammation. In a recent study of 50 patients with RA, Eijssbouts et al.22 demonstrated that under the standardized conditions of the insulin tolerance test, patients with RA have decreased plasma cortisol levels compared with healthy controls, despite elevated levels of IL-6 in these patients. Because there was no difference in ACTH levels, the authors suggest that reduced HPA axis responsiveness may be due to a defect located at the adrenal level; this contrasts with what is suggested by the data of Buske-Kirschbaum et al.24 in patients with AD. In addition, decreased activity of the HPA axis has been found in other chronic inflammatory diseases, such as Crohn disease.26

The results of our study suggest that disease activity rather than topical corticosteroid use is responsible for the low basal cortisol levels between children with moderate to severe AD regularly treated with topical corticosteroids compared with controls. In a more recent open-label safety study on the effect of fluticasone propionate cream 0.05% twice daily over 3–4 weeks in 51 children with moderate to severe AD, no effect on basal serum cortisol levels was seen.19

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serum cortisol levels in patients with severe AD. This hypothesis is supported by data from the literature, linking chronic inflammatory diseases, such as AD, RA and inflammatory bowel disease, to attenuated HPA axis responsiveness.

Measuring basal serum cortisol has its limitations as it only reflects what occurs at the level of the adrenal gland. In addition, no information is available on the responsiveness of the adrenal gland upon stimulation. A low basal cortisol level does not automatically mean that the gland is not responsive to stimulation. Further research is necessary to establish if only the adrenal gland is affected or if the suppression of this axis also takes place higher, at the level of the pituitary gland and/or hypothalamus. The results of Buske-Kirschbaum et al. suggest that the latter could well be the case in patients with AD.

These findings have major implications for daily practice when treating patients with moderate to severe AD. Although percutaneous absorption of potent topical corticosteroids is likely to occur, especially during the acute phase in severe AD, the suppressive effect on adrenal gland function seems to be overruled by the positive effect of adequate disease control. Bearing these results in mind, doctors should worry more about the effect of inadequate disease control than the possible side-effects of potent topical corticosteroids.

Finally, we advise measuring basal serum cortisol levels in patients with severe AD with uncontrolled disease, with follow-up measurements during treatment. When basal serum cortisol levels remain below normal level despite adequate treatment, corticosteroid supplementation during stressful events, such as operations, fever or after a trauma, is advised. Further studies are needed to investigate whether attenuation of the HPA axis precedes chronic inflammation in AD or can be regarded as a result of chronic inflammation.

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