Biological Sex and IgE Sensitization Influence Severity of Depression and Cortisol Levels in Atopic Dermatitis

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Short Title: Biological sex influence in atopic dermatitis

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Key Message: Immunoglobulin E, cortisol and biological sex possess distinctive and complex effect in atopic dermatitis

Keywords: Atopic Dermatitis, Cortisol, Depression, Immunoglobulin E, Testosterone

Abstract

Background

Depression is a common comorbid condition with atopic dermatitis (AD), particularly during the active disease cycle. Controversial results regarding the contribution of biological sex, immunoglobulin E (IgE) sensitization and cortisol on AD severity and comorbid depression justify further investigation.

Objective and Methods

To explore the influence of sex and IgE sensitization on biochemical and psychological parameters, and severity of AD a case-control study of 105 volunteers (56 AD, 49 healthy controls (HC); 50 males, 55 females) was conducted over 10 weeks, starting at dermatological symptoms onset. Disease severity, serum IgE, cortisol and testosterone levels, and depression scores were assessed at study baseline and after 10 weeks of conventional treatment.

Results

Dermatological severity differed among AD males by IgE sensitization and was elevated in males with extrinsic atopic dermatitis (EAD). Hamilton Depression Rating Scale (HAMD) scores were elevated in all patients at study baseline and improved with symptom reduction to HC levels, except female EAD. Severity of depression and dermatitis were correlated in EAD males at baseline and at week 10. Serum cortisol was elevated in male EAD at baseline, whereas in males with intrinsic atopic dermatitis (IAD) at week 10. In addition, cortisol levels were found negatively correlated with SCORAD and HAMD scores in EAD males at week 10.

Conclusion

Pathophysiological features of AD and depression are likely related to different inflammation-based effects and appear to be biological sex-dependent. Cortisol levels depend on biological sex and IgE sensitization in AD and increase in males with EAD at the exacerbation and IAD males at resolution.

Biological sex-related disease triggers, IgE sensitization and cortisol levels are important for the understanding of the mechanisms underlying AD and comorbid depression.

Keywords: atopic dermatitis, cortisol, depression, immunoglobulin E, testosterone

Introduction

Atopic dermatitis (AD) is the most representative example of dermatological disorders (1) with a high rate of psychiatric comorbid pathology (2-4). The link between the nervous system and skin is based in common embryogenesis from the ectoderm and both systems are regulated by the similar neuroendocrine mechanisms (5, 6). Several studies have demonstrated that stress represents a potent trigger of AD initiation or progression and influence on disease severity (5, 7, 8). A possible mechanism that contributes to dermatitis development is dysregulation of the biological stress response system by altered hypothalamic-pituitary-adrenal (HPA) axis functioning (9). HPA axis as a key regulator of stress response and its dysregulation has also been suggested to have a prominent role in various psychopathologies including depression (10-12). Comorbid depression, anxiety, and suicidal ideation are known components of AD particularly during its exacerbation (13). Attenuated response of the HPA axis to stress, mediated primarily at the pituitary level, has also been demonstrated in AD patients (14, 15). AD severity has been linked to the low basal levels of cortisol in patients with severe AD (16), which apparently can be explained by the main pathogenic mechanisms of chronic allergic diseases and the presence of greater type 2 helper T-cell (TH2) response correlated with lower cortisol levels (9, 17). Nevertheless, other studies reported no altered HPA axis function in AD patients (9, 18, 19), leaving the degree of HPA axis involvement in AD pathophysiology an open question. HPA response patterns differ markedly between males and females (20); however, few studies have investigated influence of biological sex on cortisol regulation in AD.

In addition to HPA axis activity, many studies emphasize the role of gonadal hormones in depression and AD (21). It is well known that AD is immune-mediated disease and certain alterations in sex hormone metabolism and balance can play a predisposing factor role (22). Testosterone may affect the balance between TH1/TH2, immunoglobulin E (IgE) synthesis, and eosinophil proliferation, thus modulating allergic reactions (23).

Interaction between the HPA-axis and the hypothalamic-pituitary-gonadal (HPG)-axis was also observed with increased HPA and in parallel diminished HPG activity in depressed males and females (6, 24) as well as in AD patients (22) . In women suffering from depression, lower plasma estrogen levels and increased plasma androgen levels have been observed (25), whereas testosterone levels were found decreased in depressed men (26, 27), although some studies reported no such correlation (28-30). The present study is a further reporting of prior work with AD patients (31). The aim of the current work was to explore biological sex-specific biochemical, dermatological, and psychological parameters of AD patients to provide a basis for development of improved treatment paradigms.

Materials and Methods

We conducted a case-control study of 105 patient volunteers (56 AD, 49 healthy controls (HC)) over 10 weeks of dermatological symptom presentation starting at symptom onset. Within the framework of the set goal patients were divided by biological sex and IgE sensitization. Inclusion criteria for the patients were: no unstable non-dermatological medical conditions or pregnancy; no systemic and/or topical glucocorticoid, immunosuppressant and psychotropic medications within the month prior to blood sampling; no history of mental or other dermatological disorders; no severe forms of disease, requiring systemic therapy; good general physical health. Following the first blood sample, patients were provided conventional inpatient treatments according to the international guidelines, taking into account severity of disease and anamnesis. Dermatological and psychological statuses of the patients were assessed twice: at entry point (study baseline, disease exacerbation) and at week 10. Severity of dermatitis was assessed using Scoring of Atopic Dermatitis (SCORAD) index (32). Severity of depression was assessed according to DSM-V criteria with Hamilton Depression Rating Scale (HAMD). The full version of the Materials and Methods section including sample collection and processing, laboratory tests and statistics details provided in supplementary materials.

Results

SCORAD sex differences are based on IgE sensitization

SCORAD ratings corresponded to moderate AD and did not differ between male and female patients (Figs 1A, 1B, 1C). Time-dependent improvement was noted in all patients [AD: $F(1,98)=33.11$, $p<0.001$; EAD: $F(1,56)=16.41$, $p=0.001$; IAD: $F(1,38)=24.81$, $p<0.001$]. However, within-sex differences were observed when patients were considered by disease subtype. In males, differences in both initial dermatological symptom intensity [$F(1,45)=11.30$, $p=0.002$; Fig.1D] and rate of improvement [$F(1,45)=14.34$, $p=0.001$] were noted, whereas in female patients time-dependent improvement [$F(1,49)=20.26$, $p<0.001$] was observed with no disease subtype differences in disease severity and improvement (Fig. 1E). Serum IgE levels in EAD and IAD patients were within the corresponding ranges and were not significantly changed at week 10 compared to baseline (Data not shown). Spearman analysis revealed a significant correlation between SCORAD and IgE levels in AD males at baseline and week 10, whereas in AD females only at week 10 (Table 1). When AD patients were divided by IgE sensitization, correlation was found in EAD females at baseline and week 10. In EAD males, SCORAD and IgE levels were found correlated only at week 10 (Table 1).

Depression scores and improvement differ by biological sex and IgE sensitization in AD patients

All AD patients presented with higher depression scores at baseline compared with HC (increased by: males 98%, $p<0.001$; females 120%, $p<0.001$), with AD females elevated above male scores [46% increase; $F(3,192)=28.17$, $p<0.001$; Fig. 2A]. When considered by AD disease subtype, this trend was mainly associated with the EAD group, with female depression scores elevated 60% above male scores [$F(3,150)=25.26$, $p<0.001$; Fig. 2B]. Males improved by week 10 to HC score levels, whereas females remained elevated. All IAD patients, depression scores were elevated at baseline (males 123%, females 120% increased) and improved to HC levels by week 10 [$F(1,132)=6.58$, $p=0.011$; Fig. 2C]. No differences in depression score were observed within biological sex groupings between AD subtypes, yet time-

dependent differences in score improvements by disease subtype were detected in female AD patients [F(1,49)=8.1237, *p*=0.006]. HAMD and SCORAD scores were found correlated (Spearman analysis) in EAD males at baseline and week 10 (Table1).

Elevated cortisol follows IgE increase in EAD male patients at baseline and rises in IAD males at week 10

All patient serum cortisol levels were within normal ranges, however, a link between cortisol, sex, and AD disease subtype was noted. AD male cortisol was higher at baseline (28% increase) and reduced by week 10 compared with HC [F(3,192)=5.043, *p*=0.0022; Fig. 3A]. This increase was more pronounced in EAD males (35% increase, F(3,150)=4.564, *p*=0.004; Fig. 3B). In IAD males, cortisol was elevated at week 10 [37% increase, F(3,132)=3.783, p=0.012; Fig. 3C]. No intra-sex differences between AD disease subtypes were observed (Figs 3D and 3E). Serum testosterone levels were within the normal ranges among AD patients (data not shown). No sex- or IgE-dependent correlations with testosterone were observed. Spearman analysis revealed negative correlation between cortisol levels and SCORAD scores at week 10 in AD males, reflected mainly by the same correlation in EAD subgroup (Table 1). Moreover, cortisol levels in EAD males at week 10 were also found negatively correlated with HAMD scores (Table 1). Testosterone/cortisol ratio analysis hinted at disparity among AD and HC groups [F(3,192)=3.107, *p*=0.027; Fig. 4A]; however, Bonferroni separation test did not confirm differences. Further division into AD subtypes indicated that EAD males had lower ratios (-40%) than sex-matched HC, which reached HC levels by week 10 [F(3,150)=3.039, *p*=0.031; Fig. 4B]. In EAD males at disease baseline, testosterone/cortisol ratio was significantly lower compared with EAD females (Fig. 4B). No differences were found among IAD patients (Fig. 4C). No intra-sex differences in testosterone/cortisol level were detected between AD subtypes (Figs 4D and 4E).

Discussion

In the present study we analyzed sex- and disease-specific factors which are known to be related to dermatological and psychiatric pathologies. In agreement with previous reports (33, 34), we found that severity of AD both in males and females was positively correlated with IgE sensitization, albeit at different phases of the active disease cycle. Severity of dermatological picture differs by IgE sensitization between AD males, whereas this difference is not seen in AD females. We can relate it to the hypothesis that dehydroepiandrosterone (DHEA, a testosterone metabolite) may be one of the regulators of IgE synthesis and eosinophil proliferation in patients with AD, thus modulating severity of dermatitis (23). In addition, we found that depression severity was more pronounced in EAD females compared to males. The same correlation between sex and HAMD scores was reported in another study (35). Thus, our findings may help to explain the differences between AD males and females observed here both in terms of dermatological and depression scores.

Earlier investigations implicating the role of cortisol levels in AD pathophysiology reported conflicting results, however there were no considerations of sex differences and IgE sensitization (15, 16, 36). Our findings suggest an inverse association between severity of disease and cortisol levels according to AD subtype in male patients at study baseline (disease exacerbation) and study end (disease remission). Thus, whereas in EAD males cortisol levels were higher at study baseline and reached HC levels at week 10, in IAD males cortisol was elevated by week 10. No such correlation with cortisol and any of the factors examined here in individuals emerged at disease onset. However, increased cortisone/cortisol levels have been recognized as a feedback mechanism presented in AD patients, which has also been observed to produce precursors of anti-inflammatory eicosanoids (37). Several studies reported an association between attenuated HPA-axis response and severity of AD (14, 16, 38). This corresponds with a shift toward the high end of normal cortisol levels range in IAD males and negative correlation of cortisol levels and SCORAD scores in EAD males at disease regression. Elevated cortisol serum levels in EAD patients at disease exacerbation may be explained by activated HPA-axis response caused by IgE

antibody mediated degranulation of mast cells (39). In addition, increased cortisol in EAD males may be associated with sex hormones activity. A number of *in vivo* and *in vitro* studies suggest that sex hormones regulate mast cell functionality and distribution (40). Moreover, it is known that mast cells express androgen receptors, although their role is not fully understood (41, 42). Interesting, negative correlation between cortisol levels and SCORAD scores in male patients with EAD at week 10 was observed. This correlation seems paradoxical and may be also attributed to the complex hormonal regulation in AD. This assumption is supported by the earlier study of Herrscher and colleagues suggesting that physiological levels of serum cortisol can regulate IgE-dependent cutaneous inflammation by affecting the expression of cellular events at late phase sites (43). Thus, on the basis of evidence presented here, we may conclude that cortisol regulation in AD depends on biological sex and disease subtype (IgE sensitization).

It is known that cortisol level is associated with depression (10, 11), while cortisol regulation is different and depends on depression form (44). In all AD patients in this study, depression was observed (Fig. 3), however as we mentioned above cortisol levels were presented differently by AD subtype and in a sex-dependent manner. Further, we can observe biological sex influence on severity of depression in AD, which corresponds with the results of other studies (45). Although depression scores and cortisol levels in EAD males were decreased at week 10, negative correlation between cortisol and HAMD scores was revealed in these patients. These phenomena further indicate that pathophysiology of comorbid depression in AD is a complex process and depends on biological sex and IgE sensitization. Thus, we may suppose a differential mechanism of comorbid depression in AD patients compared with major depressive disorder (MDD) patients who have elevated cortisol. Moreover, predominance of elevated depression scores in women compared with men only in EAD patients and correlation between HAMD and SCORAD scores in EAD males may link IgE to manifestation of depression in AD. Higher depression scores in MDD females have been demonstrated in several studies (6, 46). Further, cortisol

levels are also found to be higher in women with MDD (47). We assume that differences in sex- and AD disease subtype-dependent levels of cortisol may reside in differences in immune regulation under AD. Thus, sex and IgE sensitization may influence the course and mechanism of comorbid depression in AD. Testosterone and DHEA production are decreased in dermatological patients (22). Alteration of testosterone levels may be differentiated in AD patients by biological sex: no alteration in women and decreased in men (48). We did not find any significant changes in testosterone levels in AD patients, except the upward trend at week 10 (data not shown).

Cortisol has been suggested as a biological predictor of psychological variables that moderate the testosterone-behavior relationship (49, 50) and may partially explain both sex-dependent disease exacerbation and psychiatric effects. Significantly lower testosterone/cortisol ratio in EAD males compared with HC at the exacerbation stage is most probably linked with elevated cortisol levels, but due to the fact that androgens are involved in pathophysiology of AD and results of this study showed only testosterone tendency to increase at week 10, we may assume an influence on testosterone/cortisol ratio in AD. Sex differences in studied parameters of EAD patients – i) significantly higher testosterone/cortisol ratio and HAMD scores in EAD females compared with males at study baseline, ii) decline of testosterone/cortisol ratio compared with HC, and iii) elevation of SCORAD scores compared with IAD individuals in EAD males – suggest that testosterone/cortisol ratio may be linked with comorbid depression and severity of AD.

This study demonstrates distinctive and complex effect of IgE, cortisol and biological sex on severity of AD and comorbid depression. The limitation of our study is relatively small sample size, thus further studies are required to explore the link between sex differences in IgE sensitization and cortisol levels, which may be an important hallmark in etiology of AD and comorbid depression and may assist clinicians in making treatment decisions of individual patients.

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Statement of Ethics

The authors have no ethical conflicts to disclose. This study has been approved by the Astana Medical University Human Research Ethics Committee in May 2014 (AMU approval No.: 4). ClinicalTrials.gov Identifier: NCT03831646.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

This paper was planned and written in collaboration by the authors. TV, AK, GB, GA and AP performed the study design, data analysis and interpretation, and prepared the main manuscript text. TV conducted all the experiments, MK, AP and TV contributed significantly to data acquisition and analysis.

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Figure Legends

Fig. 1. SCORAD scores in atopic dermatitis. SCORAD rating of (**A**) AD, (**B**) EAD, (**C**) IAD patients.

Bars represent mean (±SEM). White bars: study baseline; Black bars, week 10. Time-dependent change in dermatological score by biological sex (two-way ANOVA): AD, $F(1,98)=33.11$, $p<0.0001$; EAD, $F(1,56)=16.41$, $p=0.0002$; IAD, $F(1,56)=24.81$, $p<0.0001$. Comparison of SCORAD ratings in (**D**) male [disease subtype: $F(1,45)=11.30$, $p=0.0016$; time: $F(1,45)=14.34$, $p=0.0005$] and (**E**) female [time: $F(1,49)=20.46$, $p<0.0001$] study baseline and week 10 AD patients by IgE sensitization.

Fig. 2. Depression scores in atopic dermatitis and healthy controls.

Bars represent mean (±SEM). White bars: study baseline; Black bars, week 10; hatched bars, healthy controls. Letters above bars are results of a Bonferroni means separation test (two-way ANOVA): (**A**) AD:[$F(3,192)=28.17$,$p<0.0001$]. (**B**) EAD: [$F(3,150)=25.26$, $p<0.0001$]. (**C**) IAD:[$F(3,132)=15.68$,$p<0.0001$]. Comparison of HAMD ratings in (**D**) male [non-significant] and (**E**) female [time: $F(1,49)=8.137$, $p=0.0063$] study baseline and week 10 AD patients by IgE sensitization.

Fig. 3. Serum cortisol in atopic dermatitis and healthy controls.

Bars represent mean (±SEM). White bars: study baseline; Black bars, week 10; hatched bars, healthy controls. Letters above bars are results of a Bonferroni means separation test analyzed within study week (two-way ANOVA): (**A**) AD:[$F(3,192)=5.043$, $p=0.0022$]. (**B**) EAD:[$F(3,150)=4.564$, $p=0.0043$]. (**C**) IAD:[$F(3,132)=3.783$, $p=0.0121$]. Comparison of (**D**) male and (**E**) female study baseline and week 10 AD patients by IgE sensitization.

Fig. 4. Rescaled testosterone/cortisol ratios in atopic dermatitis and healthy controls.

Dermatological patient data were rescaled relative to biological sex-matched healthy controls. Bars represent mean (±SEM). White bars: study baseline; Black bars, week 10; hatched bars, healthy controls. Letters above bars are results of a Bonferroni means separation test (two-way ANOVA): (**A**) AD:[$F(3,192)=3.107$, $p=0.0277$. (**B**) EAD:[$F(3,150)=3.039$,$p=0.0309$]. (**C**) IAD[non-significant]. Comparison of (**D**) male and (**E**) female study baseline and week 10 AD patients by IgE sensitization.