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CLINICAL REPORT

Psychophysiological Effects of Stress Management in Patients with Atopic Dermatitis: A Randomized Controlled Trial

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Atopic dermatitis leads to, and can be triggered by, stress. Psychological interventions have been shown to have positive effects on skin status, itch and scratching behaviour. However, it has not been analysed whether stress management leads to a change in physiological stress level and psychophysiological stress reaction under acute stress in this patient group. In this study 28 patients with atopic dermatitis were randomized to an experimental group (cognitive behavioural stress management) or a control group. The endocrine stress level and skin status were measured before and after the stress management programme. A public-speaking paradigm was used to induce acute stress. The study revealed that the experimental group had a tentatively reduced cortisol awakening response after the stress management programme. In addition, the experimental group remained calmer and showed lower salivary cortisol levels under acute stress. Thus, stress management might be a useful addition to standard treatment in patients with atopic dermatitis. ***Key words: atopic dermatitis; stress; stress management; cortisol; cortisol awakening response; psyche.***

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Atopic dermatitis (AD) is an atopic skin disease (1, 2) affecting approximately 3% of German adults (3). It is characterized by chronic, recurrent pruritus, lichenification at typical sites on the body, and by atopic comorbidity (asthma, rhinitis, or conjunctivitis) within the patient and/or his or her family (4). AD causes considerable psychological burden, including sleeping disorders, anxiety, depression, feelings of unattractiveness, and financial strain (5–8). Diverse factors, such as hereditary factors, allergens, neurogenous and immunological factors, may cause or trigger AD (9, 10).

Psychological stress is also thought to be very important in AD; an assumption which is supported by clinical observation and epidemiological and correlative studies (11–19). In addition, patients with AD differ from healthy controls in their reaction to laboratory stress and experience a worsening of the skin after exposure to stress (20–24).

The observed relationship between stress and AD thereby raises the idea of investigating the effectiveness of stress management programmes as a possible treatment strategy in AD.

Cognitive behavioural stress management programmes (CBS) have been shown to reduce cortisol responses to laboratory stress in healthy participants and patients with rheumatoid arthritis and to improve psychological and immunological functions in patients with HIV (25–29). The few studies evaluating psychological interventions (some of which also include stress management) in patients with AD found positive effects on skin status as well as on itch and scratching behaviour (30–38). In most of these studies, however, comprehensive and disease-specific programmes were applied. Only one older study analysed the effects of a widely disease-unspecific programme and found benefits in clinical and psychological well-being (35).

The aim of the present study was to replicate these favourable effects and to extend the analysis to hypothalamic-pituitary-adrenal-axis (HPA) responsiveness as physiological stress indicator. We hypothesized that CBS training, compared with a waiting list control, would reduce HPA reactivity to awakening (Hypothesis 1), improve skin status (Hypothesis 2) and reduce HPA-reactivity and psychological stress responses to acute stress (Hypotheses 3a and 3b).

MATERIALS AND METHODS

Participants

Patients with AD were recruited through announcements in the newspaper and at the campus of the University of Gießen, Germany. They were offered free participation in a CBS and €150. The following criteria were applied in order to ensure that only those patients who exclusively had AD were included and to minimize the influence of other factors on the endocrine parameters. The inclusion criterion was: diagnosis of AD following the Hanifin & Rajka criteria (4). Exclusion criteria were: absence of AD symptoms for more than one year, use of more than 10 g/month of steroid-containing ointments, chronic psychiatric or other somatic diseases (including asthma), chronic medication, acute symptoms of rhinitis, infectious diseases, use of antibiotics, inoculations 4 weeks prior to the study, a body mass index < 18 or > 30, drug abuse, work in 3 shifts, prior participation in a study including stress induction or in a stress management programme,

pregnancy or lactation. In another study comparing gingival immune responses of participants with and without AD, further selection criteria related to oral health: patients had to show clinical evidence of gingivitis (prevalence of gingivitis exceeds 90% in Germany and most other Western communities (39)) and were excluded if they had untreated caries, periodontitis, or underwent dental or orthodontic treatment during the study. Fig. S1 (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1415) shows the CONSORT (Consolidated Standards of Reporting Trials) diagram.

Independent variable

Randomization was conducted using identical-looking cards placed in opaque envelopes indicating the respective condition. After inclusion of the participant, a person not in contact with the participant drew a card and assigned the respective condition to the participant; the condition was concealed from all researchers involved in the assessment of dependent variables. The experimental group (EG) took part in a standardized CBS (42) in groups of 6–8 participants, half of whom had AD while the other half did not. The CBS was performed by a certified female psychologist in 4 3-h sessions within a 2-week period. The programme focuses on cognitive restructuring and enhancing problem-solving strategies. It includes an emergency plan for an acute stress situation and contains elements of Jacobson's progressive muscle relaxation. Three weeks after the final lesson, a booster-session was conducted in order to refresh and internalize what had previously been taught. The control group (CG) was offered the same CBS at the end of the study.

Dependent variables

SCORAD. The clinical severity of AD was assessed by means of the SCORAD (40). None to mild AD is indicated by scores below 25, moderate AD by scores between 25 and 50, and severe AD by scores above 50. The SCORAD maximum is 103 (41). The SCORAD was measured by a trained doctoral student (CS), calibrated by a dermatologist before the beginning of the study.

HPA-reactivity. To assess HPA-reactivity, salivary cortisol was assessed during and after acute stress, and in the morning to determine the cortisol awakening response (CAR). Saliva was sampled for 3 min, either in glass beakers and subsequently transferred to Salivettes (acute stress), or directly by means of Salivettes (CAR; Sarstedt, Germany). To determine the CAR, participants were instructed to collect saliva immediately after awakening and 30 min afterwards on 2 consecutive days (43). Participants were asked to sleep for at least 6 h and to wake up between 06.00 h and 08.00 h. To avoid any contamination, participants were instructed not to brush their teeth, eat, drink, or smoke until they had taken the second saliva sample of the day. They were further asked to avoid physical activity and consumption of alcohol the day before. The scores for the CAR were determined by subtracting the cortisol level 30 min after awakening from the score measured immediately after awakening. This was done for both days. The mean for the 2 consecutive days was then calculated to minimize error variance. Samples were stored at –20ºC prior to biochemical analysis. Cortisol concentrations were determined by a commercial enzyme-linked immunosorbent assay (ELISA; IBL-Hamburg, Germany). All analyses were performed in duplicate within the same lot to avoid high inter-assay variation. The intra-assay variation was below 5% in 95.7% of the samples, below 10% in 3.7% of the samples, and below 11.5% in 0.6% of the samples.

Psychological stress response. To assess psychological responses to acute stress, participants completed the Multidimensional Mood Questionnaire (MDMQ), which measures "Mood," "Alertness," and "Calmness" prior to and after acute stress (44).

Control variables

As control variables, the Trier Inventory of Chronic Stress (TICS) (45) and the German version of the Hospital Anxiety and Depression Scale (HADS) (46) were assessed at baseline, as was the serum immunoglobulin E (IgE) concentration, which allows for differentiation between extrinsic and intrinsic AD. An IgE level higher than 150 kU/l indicates the extrinsic type of AD, while an IgE-level lower than 150 kU/l indicates the intrinsic type of AD (47).

Procedure

The study lasted 10–14 weeks in total and was divided into 4 study periods: baseline (week 1); CBS (weeks 2–8); measurement of basal effects of the CBS (week 9); induction of acute stress (weeks 10–14). At baseline, participants were instructed how to collect saliva for later assessment of the CAR. In weeks 1 and 9, the SCORAD as well as the CAR were assessed. During the induction of acute stress (weeks 10–14), salivary cortisol and mood were assessed.

The TICS and HADS were also measured at baseline. In addition, blood samples were taken to determine the IgE level.

During the intervention period, members of the EG took part in the CBS (see independent variable), while members of the CG were not treated during that time.

After the booster-session of the CBS, a minimum of 3.5 and a maximum of 7.5 weeks elapsed before the patients were subjected to an acute laboratory stress paradigm, which has been proven in several studies to consistently induce cortisol and subjective stress responses (48, 49). The stress situation takes place in an observation laboratory. The stressor consists of an anticipation period (10 min), after which participants are informed that their task is to give a speech in front of a camera. At the beginning of the subsequent preparation period (10 min), they are informed of the topic of the speech ("My good and bad personal characteristics, how they influenced me and my life") and the 9 quality criteria their speech should fulfil (which are difficult to accomplish). For the speech (10 min), participants have to stand in front of a camera and are instructed via an intercom. Two minutes after beginning their speech, the participants are interrupted and reminded of the quality criteria.

The time of day of the acute stress induction was kept constant for all participants. It began with a baseline period of 90 min, at the end of which the first saliva sample was taken and the MDMQ scales were assessed. The stress induction then began and saliva samples were taken every 18 min until 105 min after the stress. The only exception was the sixth measurement, which took place 36 min after the fifth. MDMQ scales were assessed again immediately after the stress. The whole session lasted from 12.00 to 16.00 h.

Ethics

The study design was approved by the ethics committee responsible. The study protocol conformed to the Declaration of Helsinki. All participants provided written, informed consent to the study and were free to withdraw at any time.

Statistical analyses

Statistical analyses were performed using SPSS 19. Kolmogorof-Smirnov Goodness of Fit Tests indicated no violation of the normal distribution assumption for any variable. Outlying scores were defined as mean ± 3 standard deviation of the respective group mean and were removed from analyses. Baseline differences between groups were assessed by *t*-tests. To analyse CBS effects on basal endocrine and clinical parameters, one-way analyses of covariance with factor group (EG vs. CG) and the respective baseline measures and gender as covariates were conducted (Hypotheses 1 and 2). To analyse the effects of CBS on acute endocrine and psychological stress responses (Hypotheses 3a and 3b), 2-factorial (group by time) analyses of covariance with the measure immediately prior to stress and gender as covariates were computed. Greenhouse-Geisser corrections were applied and original degrees of freedom with Greenhouse-Geisser ε are reported.

The original study protocol aimed to recruit 50 patients in order to achieve a power of 80% with a given significance level of 5% for large effect sizes (f = 0.41). However, a considerable number of potential participants were excluded and the final number was 28 patients. We decided to conduct the study irrespective of the small sample size in order to obtain an initial impression of the treatment effects. Accordingly, we decided to accept $p \leq 0.10$ as a tentatively significant effect. Thus, effect sizes of f = 0.55 (in the case of repeated measures of f = 0.43) become detectable as significant and of f = 0.48 (in case of repeated measures of f = 0.37) as tentatively significant with a power of 80%.

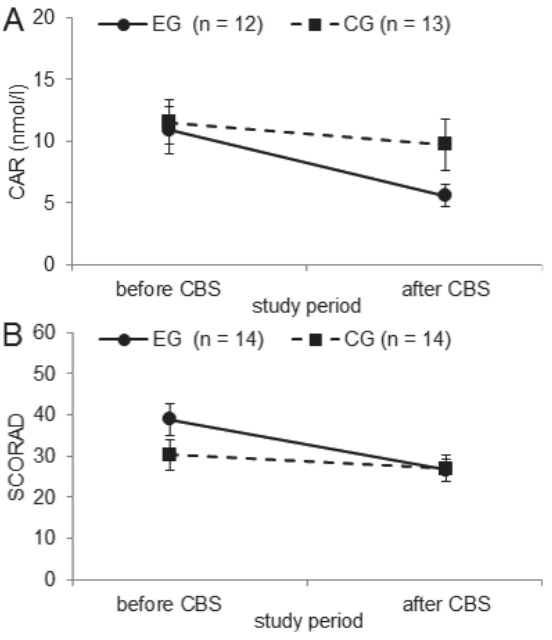

Fig. 1. Effects of cognitive behavioural stress management (CBS) on (A) cortisol-awakening response (CAR) and (B) SCORAD (Severity Scoring of Atopic Dermatitis). Means and standard errors of the mean are shown for patients who took part in the CBS (experimental group; EG) during the study and patients in the waiting list control group (CG). A tentatively significant ($p < 0.10$) group difference is observed for the CAR but not the SCORAD.

RESULTS

Patient characteristics

Four male and 10 female participants were included in each group. Groups did not differ in socio-demographic data (age, education-level), extrinsic vs. intrinsic AD, anxiety or depression scores (HADS), or in baseline chronic stress-level (TICS), CAR, or SCORAD (Table. SI; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1415).

Cognitive behavioural stress effects on the basal endocrine stress level and skin status

Three participants (2 in the experimental group) did not follow instructions for saliva collection in the morning and were thus excluded from analyses. For the remaining participants, a tentative main effect of group [F (1/21) = 3.74; $p = 0.067$; $\eta^2 = 0.151$] was observed, with tentatively reduced CARs in members of the experimental group (Fig. 1).

No group difference was observed with respect to the SCORAD ([F (1/24) = 1.916; $p = 0.179$; $\eta^2 = 0.074$]; Fig. 1).

CBS effects on the endocrine and psychological stress reaction under acute stress

Twenty-five cases could be considered in the statistical analyses of the endocrine stress reaction. One male in the experimental group and one female in the control group did not produce enough saliva, while another female EG patient showed outlying cortisol values.

Fig. 2 demonstrates that the experimental group had a lower salivary cortisol level during acute stress than the control group (group effect: [F (1/21) = 4.536; $p = 0.045$; $\eta^2 = 0.178$]). The time*group-interaction did not become significant [F (1,895/39,801) = 1.895; $p = 0.165$; $\eta^2 = 0.083$; $\varepsilon = 0.474$].

With respect to their psychological response to stress, a significant group difference was found for calmness [F (1/24) = 10.778; $p = 0.003$; $\eta^2 = 0.310$], while no further group effects were observed on the MDMQ scales.

DISCUSSION

To our knowledge this is the first study to show that a CBS reduces HPA reactivity and psychological responses to acute stress in patients with AD. In spite of these effects on physiological and psychological data, no effect was observed for the SCORAD. Thus, our hypotheses can only be accepted in part.

Similar to the results of other studies (25, 26, 29), our CBS also led to lower cortisol secretion under acute stress. However, we did not find a corresponding benefit for clinical data. Several explanations may hold for this result. First, the sample size (to be discussed later) might have been too small to detect an effect on the SCORAD: indeed, visual inspection of results shows that there is a decline in the SCORAD in the experimental group, which parallels the decline in the CAR. No such alterations are

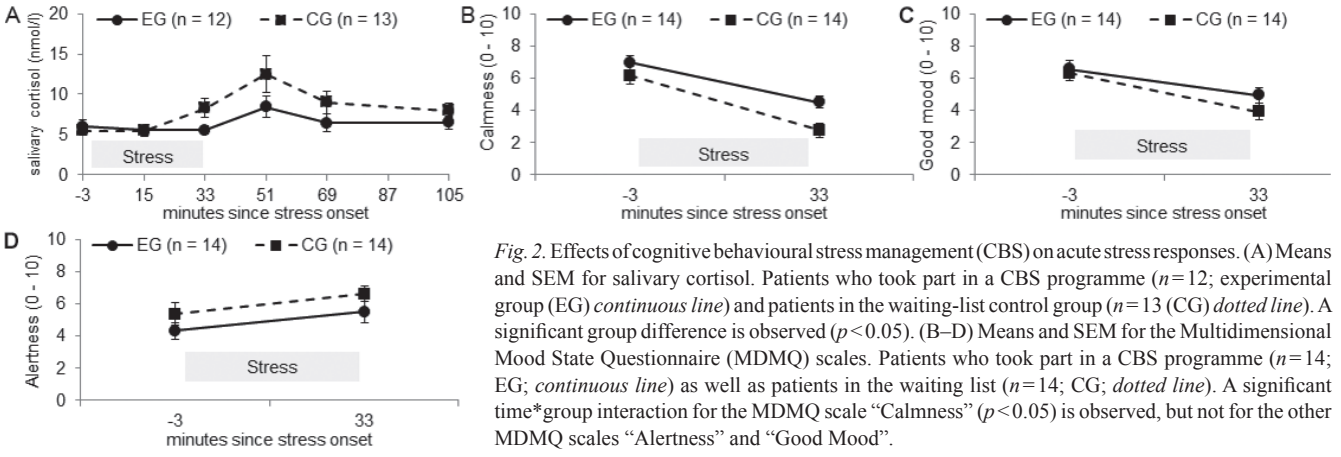

Fig. 2. Effects of cognitive behavioural stress management (CBS) on acute stress responses. (A) Means and SEM for salivary cortisol. Patients who took part in a CBS programme ($n = 12$; experimental group (EG) *continuous line*) and patients in the waiting-list control group ($n = 13$ (CG) *dotted line*). A significant group difference is observed ($p < 0.05$). (B–D) Means and SEM for the Multidimensional Mood State Questionnaire (MDMQ) scales. Patients who took part in a CBS programme ($n = 14$; EG; *continuous line*) as well as patients in the waiting list ($n = 14$; CG; *dotted line*). A significant time*group interaction for the MDMQ scale "Calmness" ($p < 0.05$) is observed, but not for the other MDMQ scales "Alertness" and "Good Mood".

observed in the control group. Secondly, it may be that a longer time is needed to detect clinical benefits. Other studies describing positive effects of psychological treatments on clinical parameters assessed these at least 8 weeks or even 1 year after the intervention (34, 35, 37). Thirdly, the participants in our study had no comorbidity with other atopic and/or somatic or psychiatric diseases. Other studies did not restrict their samples in the same way (32, 33, 35, 37). It might be that clinical benefits would be observed in groups showing at least some comorbidity. Finally, in contrast to other studies (32–35, 37), our treatment groups consisted of AD patients and participants not affected by any skin disease. One might assume that the CBS is more effective in more homogenous groups with the same disease. This would allow participants to focus on disease-related problems in their discussions (e.g. anxiety concerning the use of topical steroids, scratching alternatives). They might also profit to a greater extent from social interactions in the group, because they might feel less embarrassed talking about intimate disease-related issues, such as feelings of unattractiveness and being socially excluded.

The CBS employed in this study focuses on cognitive re-framing, which follows the idea that instead of letting irrational, stressful thoughts arise automatically, stress-reducing thoughts should be learned (50). Such strategies have been shown to have positive effects in dementia care givers (51). Furthermore, it was shown that primary appraisal of the situation, which might be altered by cognitive reframing, and reactivity to social evaluation were able to predict cortisol responsiveness to acute stress (52). However, one could argue that the relaxation training alone could explain the effects observed. Indeed, in healthy subjects mere progressive muscle relaxation (PMR) led to lower salivary cortisol (53, 54). However, in AD patients no physiological effects of mere relaxation training were observed (55).

When evaluating CBS effects, the time between the CBS and the induction of stress plays a major role. Changes in immunological (56, 57) as well as endocrine (25, 26) parameters are more pronounced in long-term follow-ups than immediately after the CBS. The time between the booster session of our CBS and induction of acute stress ranged from 1 to 2 months and cannot be considered as a long-term follow-up. To increase the effects of the CBS with regard to the SCORAD and the CAR, it might have been useful to add a long-term follow-up at least 3 months after the booster session. On the other hand, this investigation would probably have decreased the compliance of the patients.

A major limitation of the present study is its small sample size of only 28 patients. This was due to the high proportion of excluded patients. Almost 20% of interested persons were excluded because of other atopic comorbidity. This reduces external validity and hinders generalization to other populations, such as AD patients who have more than one atopic disease during their lives (58). To increase the external validity, it might be opportune to include patients with more atopic diseases in future studies and to consider the occurrence of more than one atopic disease as a covariate. A related limitation lies in the fact that the small sample did not allow the analysis of CBS effects in subsamples: for example, it would have been of great interest to differentiate between males and females, or the two types of AD. Gender should be regarded as a moderator, because it was shown that men and women differ in their cortisol response to acute stress (26, 59) and prefer different coping strategies (60, 61). Furthermore, in a previous study, a low IgE level, and thus the occurrence of the intrinsic type of AD, was a predictor of a good outcome in psychological treatment of AD (62). It was also pointed out (63) that an immunological reaction to psychological stress occurred only in patients with extrinsic AD. These studies indicate that a fundamental next step would be to analyse whether changes in responsiveness occurred in patients with these different types of AD. It is important for such a study design, however, that gender and type of AD seem to be confounded; the intrinsic type of AD occurs more often in females (64).

In summary, our study demonstrates that a short-term CBS is effective in patients with AD, at least in reducing

endocrine and psychological stress responses. Though no immediate effect on skin parameters was observed in this study, the training might be considered as an add-on to other therapeutic approaches in order to help patients cope better with stress. In addition, our study stimulates future research in order to further analyse long-term effects of such a training programme on skin parameters and to identify subgroups of patients for whom this treatment strategy is especially helpful.

The authors declare no conflicts of interest.

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