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Topical Antimycotic Treatment of Atopic Dermatitis in the Head/Neck Area

A Double-blind Randomised Study

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In order for us to evaluate the effect of topical antimycotic treatment in patients with atopic dermatitis affecting the head and neck area, 60 patients (36 females and 24 males; median age 28 years; range 14–53 years) were included in a double-blind study during 6 weeks. Of the 53 evaluable patients, 55% had positive skin prick tests to *Pityrosporum ovale*. In addition to oral antibiotic treatment, patients in group A ($n = 26$) were given miconazole-hydrocortisone cream and ketoconazole shampoo, whereas patients in group B ($n = 27$) were given hydrocortisone cream and placebo shampoo. At the start of the study *P. ovale* cultures were positive in 83% of all patients (no significant difference between the groups). After 4 weeks of treatment, there was a decrease in *P. ovale* colonisation in group A ($p < 0.001$) but not in group B. Patients in both groups improved ($p < 0.001$). The decrease in eczema score did not differ between group A and group B after 4 weeks' treatment. A further decrease of the eczema score was seen in both groups at the end of the study, but no difference was found between the groups.

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The role of environmental allergens as triggering factors in patients with atopic dermatitis (AD) has become an important field of research, since in the pathogenesis of AD dermal sensitisation within the IgE system to e.g. aeroallergens, foods and micro-organisms seems important (1–3). Among micro-organisms, *Staphylococcus aureus, Candida albicans* and *Pityrosporum ovale* have attracted attention. The role of *S. aureus* is not clear, but AD patients are often colonised with *S. aureus* (4). In a study by Savolainen et al., severe cases of AD with gastrointestinal growth of *C. albicans* were associated with IgE synthesis against *C. albicans* (5). In atopic children, associations with *P. ovale* and *C. albicans* RAST have been found (6), and cross-reacting antigens in *P. ovale* and *C. albicans* were seen in a small group of AD patients (7). Differences in the clinical picture, capacity for IgE production, frequency of food allergies and propensity to develop other atopic diseases make the group of AD patients heterogeneous (8–10). One subgroup of adult AD patients, those with so-called head and neck dermatitis (HND), show dry, itchy, erythematous lesions involving the scalp, face, neck and upper chest. The lipophilic yeast *P. ovale* is found as a part of the normal microflora in most adult persons, preferentially colonising the head and neck area (11). Immunological studies have shown specific IgE to *P. ovale* in patients with AD and most often in the subgroup with HND (12–18). Patients with HND and a positive skin prick test (SPT) to *P. ovale* showed a favourable response when they were treated with *oral* ketoconazole (19). To evaluate the effect of antimycotic *topical* treatment, we have treated patients with HND in a double-blind study with miconazole-hydrocortisone cream and ketoconazole shampoo versus hydrocortisone cream and placebo shampoo.

MATERIAL AND METHODS

Patients

Sixty patients (36 females and 24 males; median age 28; range 14–53 years) with AD involving the scalp, face, neck and upper chest (HND) were included. AD was defined according to criteria suggested by Hanifin & Rajka (20). Most of the patients also had eczema on other parts of the body. AD had started in 40 of the patients during the first year of life. A past or present history of respiratory atopy was found in 37 of the patients. All patients were consecutive outpatients seen at the Department of Dermatology, Sahlgrenska University Hospital. The first 9 patients were included in April-May 1993 and the rest of the patients from August 1993 to March 1994. Antibiotics, antimycotics and UV-treatment were not permitted for 3 weeks before starting the trial. The study was approved by the Ethics Committee of Sahlgrenska Hospital. Dactacort®, Fungoral shampoo® and placebo were supplied without any financial support by Janssen Pharmaceutica, Gothenburg, Sweden.

Experimental design

In a double-blind, randomised, controlled study, patients were allocated to one of two treatments (for the affected area head, neck and upper back). Patients in group A were treated with miconazole-hydrocortisone cream (Daktacort®) and ketoconazole shampoo (Fungoral shampoo®), patients in group B with hydrocortisone cream and a placebo shampoo (Fungoral shampoo base). The cream was applied twice daily and the shampoo was used twice weekly. Emollients were permitted throughout the study. The duration of the study was 6 weeks, with follow-up visits in week 4 and 6. Healed patients stopped the treatment after 4 weeks and patients who deteriorated after 4 weeks were considered treatment failures. During the first 2 weeks of the study, all patients were treated with flucloxacillin tablets 750 mg twice daily, or, in case of allergy, with erythromycin 500 mg twice daily. If eczema on other parts of the body was severe, this was treated as before the study (mild to potent corticosteroids). The amount of study medicine used was measured at the first return visit.

Scoring of atopic dermatitis

All evaluations were made by the same observer (A.B.) at the start of the study, after 4 weeks and after 6 weeks. The SCORAD index for assessment of atopic dermatitis was used (21). However, the protocol was modified due to the design of the study, in which only the head, neck and upper part of the trunk were studied. The extent was evaluated as 100% if the above-mentioned area was covered and proportionally less with decreasing area involved. With this design, the weight given to each item remained 20% for extent, 60% for intensity and 20% for subjective symptoms, which is the design of the composite score in the SCORAD index. Instead of the item sleep loss, patients evaluated overall condition (dryness, burning sensation) in the affected area.

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Table I. *Patient characteristics at the start of the study*

	Group A	Group B
Number of patients	26	27
Sex	16F 10M	14F 13M
Age, years range (median)	14–53 (29)	16–42 (28)
Other atopic manifestations	18/26 (69%)	19/27 (70%)
IgE range, kU/l (median)	$n=25$ <2–12300 (1300)	$n=25$ <2–19300 (370)
SPT positive to *P. ovale*	13/26 (50%)	16/27 (60%)
P. ovale culture positive	23/26 (88%)	21/27 (78%)
No. of CFU *P. ovale*, median	9	4
Bact. cult. pos. for *S. aureus*	20/24 (83%)	24/27 (89%)
Eczema score range (median)	36.70–84.30 (58.60)	37.40–92.30 (60.10)

Serum IgE

Concentrations of total serum IgE were determined by radioimmunoassay (RIA) (Pharmacia IgE RIA 100, AB, Uppsala, Sweden), following the recommendations of the manufacturer. The result is in kU/l.

Skin prick test

An SPT was performed on the forearm with a water-soluble extract of *P. ovale*, protein concentration 5 mg/ml (ALK Laboratories, Denmark). The result was evaluated in relation to a histamine reference, equivalent to histamine hydrochloride 10 mg/ml, and regarded as 3+ if the wheal was equal to the histamine skin reaction. A skin reaction of ≥2+ or 3 mm or more was regarded as positive (22).

P. ovale culture

Cultures were taken from the forehead. Samples were obtained using contact plates (*P. ovale* Maxiplate, Max Lab Diagnostic HB, Kållered, Sweden) (23). This contact plate contains peptone, bacto agar, glucose and yeast extract. Lipid supplements were ox bile, glycerol, glycerol monostearate, Tween-60 and cow's milk. Antimicrobial supplements were chloramphenicol and cycloheximide. The contact plate was pressed against the forehead skin for 15 s, incubated in a plastic bag at 37° and read after 6 days. Results were expressed as numbers of colony forming units (CFU).

Culture for other fungi

Specimens for culture of other yeasts and dermatophytes were transferred to Sabouraud's agar without supplements and dermatophyte test media (DTM) for up to 3 weeks.

Bacterial culture

Material for bacterial culture was taken with a cotton swab and transferred to a blood agar plate and read after 24 h.

Statistics

We used the following tests: Mann-Whitney U-test for differences between groups, Wilcoxon's test for differences within groups and Spearman rank correlation. For qualitative data, chi^2 was used.

Table II. *Number (n) of patients healed, eczema score, median and (range), in the two groups*

Group A, n = 26. Group B, n = 27.

SCORAD	Group A	Group B
Baseline	58.60 (36.70–84.30)	60.10 (37.40–92.30)
After 4 weeks	33.20 (0–71.20)	22.90 (1.40–90.20)
End of study	18.75 (0–71.20)	16.45 (0–90.00)
Healed at 4 weeks	n= 5	n = 2
Healed at 6 weeks	n = 2	n = 6

RESULTS

Of the 60 patients enrolled, 7 patients were excluded from the study. Two patients were lost to follow-up. One patient deteriorated severely some days after the first visit. One patient never started the antibiotic treatment and 3 patients stopped antibiotic treatment after some days because of side-effects (urticaria in 2 cases, gastrointestinal problems in one case). Of the 7 excluded patients, 4 belonged to group A and 3 to group B. Of the remaining 53 patients, 26 belonged to group A and 27 to group B. The groups did not differ at the start of the study on any of the parameters, as described in Table I.

All the 53 evaluable patients completed 4 weeks' treatment and 43 completed 6 weeks' treatment. Seven patients healed after 4 weeks' treatment and continued only with emollients. Two patients (one from group A and one from group B) deteriorated and stopped the treatment after 4 weeks, and one patient from group B was unable to come back for the last visit.

During the study, 15 patients healed; 7 after 4 weeks and 8 after 6 weeks of treatment. Of the patients who healed, 7 belonged to group A and 8 to group B. After 4 weeks' treatment, the reduction of the eczema score was significant ($p<0.001$) in both groups. The decrease in eczema score did not differ between group A and group B. A further decrease of the eczema score was seen in both groups at the end of the study, but there was no difference between the groups (Table II).

Except for *C. albicans* cultured from 2 patients, no other fungi were found among the patients.

P. ovale culture at the start of the study was positive in 83% of all 53 patients, with no difference between the groups (Fig. 1). After 4 weeks' treatment, positive cultures were found in 50% in group A and in 93% in group B. The decrease in number of colonies was significant in group A ($p<0.001$) but not in group B. In group A, 10 patients became negative for *P. ovale* at the end of the study, in comparison with group B, where 3 patients became negative. Among the 10 patients in group A who became negative, 3 healed. There was no correlation between the number of *P. ovale* at the start of the study or the decrease in number during the study and the improvement of eczema in group A or group B.

The amount of cream used during the first 4 weeks of the study did not differ between the groups (median 50 g, range 15–160 g in group A; median 50 g, range 10–130 g in group B).

The SPT to *P. ovale* was positive in 55% of all patients (group A 50%, group B 60%). The SPT result correlated with the eczema score at the first visit ($r=0.29$, $p<0.05$). Total serum IgE correlated with the SPT result ($r=0.35$, $p<0.05$). There was no correlation between the SPT result and the decrease in eczema score.

One patient from group A, whose AD cleared during the study, developed an acneiform eruption, probably as a side effect of the treatment. Two patients, one from group A and one from group B, deteriorated during the first 4 weeks of treatment, and further epicutaneous tests will evaluate a possible connection with the topical treatment given.

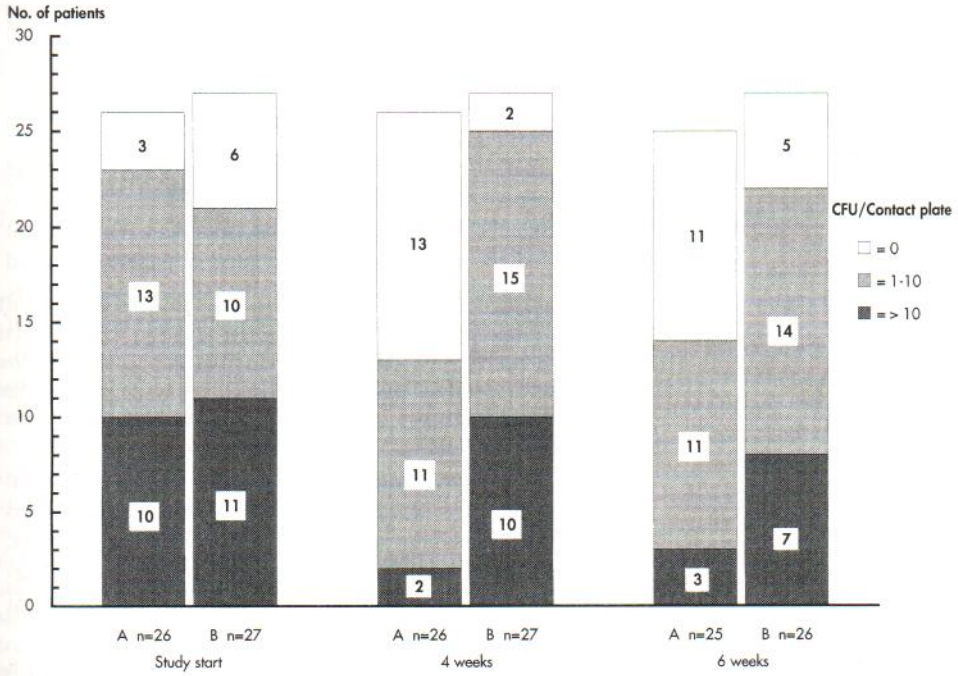

Fig. 1. Pityrosporum ovale culture at the start of the study and after 4 and 6 weeks in patients with (group A) and without (group B) topical antifungal drugs. Number of colony forming units (CFU)/contact plate.

DISCUSSION

AD affecting the adult often involves the upper part of the chest, neck and head, the area with the highest amounts of the lipophilic yeast *P. ovale*, a saprophyte belonging to the normal microflora of most adults (11). Since Clemmensen & Hjorth successfully treated patients with HND with positive SPTs to *P. ovale* with oral ketoconazole (19), no study concerning antimycotic treatment in HND has been published. The ability of *P. ovale* to trigger the production of specific IgE antibodies has been shown both as positive RAST in atopic patients and as positive SPTs (12–18). Of patients with atopic diseases those with AD are most often sensitised to *P. ovale*, especially those with involvement of the head and neck area (12, 14–16). Topical antimycotic treatment in HND is commonly used in everyday practice, even though no controlled studies have been performed. If *P. ovale* is of importance in patients with involvement of an area where this yeast is found most often, a topical antimycotic would be expected to be an important part of the treatment. The majority of our patients (group A 83%, group B 89%) were colonised with *S. aureus*, which is in accordance with other studies (4). Antibacterial treatment often has a good effect in AD, indicating that *S. aureus* is involved in the pathogenesis of AD (4). We tried to eliminate the possible effect of *S. aureus* with oral antibiotic treatment in both groups. Since ketoconazole has been shown to have not only an antimycotic but also an anti-inflammatory action (24), we treated all patients in the study with a mild steroid cream.

In this study, Daktacort® and Fungoral shampoo® were effective in significantly reducing the number of *P. ovale* ($p < 0.001$) when cultures were taken from the forehead with a contact plate. In the control group, treated with hydrocortisone and placebo shampoo, the decrease in *P. ovale* was not significant. Eczema improved significantly in both groups. However, neither the number of patients who healed (7 in group A and 8 in group B), nor the decrease in eczema score, after 4 weeks or at the end of the study, differed between the groups. Even in patients whose *P. ovale* cultures became negative during the study, eczema scores were not significantly lowered when compared with the decrease of eczema scores in patients with positive *P. ovale* culture after treatment.

Of the 53 patients selected for this study, positive SPTs to *P. ovale* were found in 55%. In patients aged 0–20 years with AD without any predilection for the area involved, we found positive SPTs to *P. ovale* in 15% (15). Findings of specific serum IgE are not always of clinical significance. This is clearly illustrated by the difficulty in interpreting the clinical relevance of RAST or SPT results to foods in children with AD, where an elimination diet is sometimes indicated. The reason why we found no difference between our two groups could be that specific IgE to *P. ovale* merely reflects the fact that the damaged skin in AD in this region enables sensitisation to the normal microflora to occur but without further clinical significance. The selection of patients for this study differed from that of Clemmensen & Hjorth (19). Their patients were all SPT-positive to *P. ovale* with eczema localised only to the head and neck area. Most of our patients also had eczema on other parts of the body, a clinical picture that we think is the most common since HND, in our experience, often indicates a severe atopic disease persisting into adult life. In our investigation, the SPT result did not correlate with improvement of eczema. Topical antimycotic treatment may also be less effective than systemic treatment in reducing *P. ovale*, since the yeast colonises hair follicles. Since cross-reacting antigens have been found in *C. albicans* and *P. ovale*, gastrointestinal colonisation of *C. albicans* may still persist as a trigger for the eczema, in spite of topical antimycotic treatment (5). Finally, because the material comprised only 26 index subjects and 27 controls minor effects of the topical

antimycotic treatment cannot be ruled out. New generations of antimycotics, topical or systemic, may therefore be of interest in future studies.

The design of the study did not enable us to determine if topical antimycotics can act prophylactically, as has been shown in seborrhoeic dermatitis (25).

In conclusion: to evaluate the effect of antimycotic topical treatment, we have treated patients with HND in a comparative double-blind study with miconazole-hydrocortisone cream and ketoconazole shampoo versus hydrocortisone cream and placebo shampoo. Although *P. ovale* decreased significantly in the group given the antimycotic treatment, we did not find any significant difference in treatment results, as measured by change in eczema scores (SCORAD), between the two groups.

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