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Superantigens of *Staphylococcus Aureus* Colonization in Atopic Dermatitis and Treatment Efficacy of Oral Cefuroxim in Vietnamese Patients

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Abstract

BACKGROUND: Atopic dermatitis (AD) is a common, chronic, relapsing, genetically determined inflammatory skin disorder. Staphylococcus aureus (S. aureus) plays an important role in the pathogenesis of AD. Atopic skin is susceptible to infection with *S. aureus*.

AIM: This study was aimed to compare the skin *S. aureus* colonisation status and its secretion of superantigens in adult AD and healthy subjects and to evaluate the efficacy of two treatment regimens (oral cefuroxime plus topical betamethasone dipropionate 0.05% versus topical betamethasone dipropionate 0.05%) in AD patients.

METHODS: A group of 128 AD and 40 healthy subjects were recruited in this study and treatment efficacy was assessed by the SCORAD score.

RESULTS: *S. aureus* was found in skin lesions in 83.8% of AD patients while only 37.5% of healthy subjects possessed this kind of bacteria in the external nares ($p < 0.001$). Superantigen production was more common in *S. aureus* strains isolated from AD than the control group (58.6% versus 6.6%, $p = 0.0006$) and staphylococcal enterotoxin B was predominant (88.89%). 68 AD patients who had positive cultures with *S. aureus* were included in a clinical therapeutic trial. The isolated bacteria were all sensitive to cefuroxime. Patients were randomised to receive either oral cefuroxime 500 mg b.i.d. Plus topical betamethasone dipropionate 0.05% twice daily for 2 weeks (so-called group 1, 36 patients) or only topical betamethasone dipropionate 0.05% twice daily for 2 weeks (so-called group 2, 32 patients). The mean SCORAD scores of group 1 at baseline and after 1 and 2 weeks of treatment were 44.61, 26.69 and 16.61, respectively. The corresponding values for group 2 were 43.03, 32.53 and 23.41, respectively.

CONCLUSION: The reduction in SCORAD scores was significantly higher in group 1 than group 2 in comparison to the baseline value of each study group ($p = 0.003$ after 1 week and $p < 0.001$ at the end of treatment).

Introduction

Atopic dermatitis is a common chronic inflammatory skin condition. The prevalence varies from 10% to 20% of children. The aetiology and pathogenesis of AD have not been completely understood, leading to many problems in its management. High recurrence rates contribute to increasing the prevalence of AD.

In the late 20th century, Cork [1], Abeck [2], and Shuichi [3] found that *S. aureus* plays a very important role in the pathogenesis of AD through the production of superantigens including staphylococcal enterotoxins A and B, and toxic shock syndrome toxin-1 [4], [5], [6]. These superantigens penetrate the skin barrier and contribute to the persistence and exacerbation of skin inflammation through the stimulation of massive T cells [7], [8].

Materials and Methods

Study populations: 128 AD patients were enrolled in our study during their visits to the Hospital of Dermato-Venereology in Ho Chi Minh City from August 2010 to August 2012. There was no selection of patients by gender, localisation and severity of lesions. Voluntarily informed consents in writing were obtained from all participants. AD was diagnosed according to Hanifin and Rajka's criteria, and AD severity was based on the SCORAD index. Clinical symptoms and SCORAD scores were regularly monitored at the end of week 1 and 2, and the culture of skin lesions was carried on at the end of week 2. The control group consisted of patients without personal or family history of skin or allergic diseases who visited the Dermatological Outpatient Clinic for other reasons during the same period.

AD patients were all over 12 years old and didn't have any infected skin lesions. Those who had positive cultures with *S. aureus* were recruited in a clinical therapeutic trial. All isolated bacteria were sensitive to cefuroxime on the antimicrobial susceptibility test. Patients were equally randomised to receive either oral cefuroxime 500 mg b.i.d. Plus topical betamethasone dipropionate 0.05% twice daily for 2 weeks (so-called group 1) or only topical betamethasone dipropionate 0.05% twice daily for 2 weeks (so-called group 2). A total of 74 AD patients were eligible for this clinical trial (37 patients in each group).

Exclusion criteria included treatment with topical antibiotics in the past two weeks; oral or intravenous antibiotic treatment in the previous 4 weeks; presence of severe heart, liver, lung diseases, or immunodeficient condition (AIDS, diabetes mellitus, utilization of immunosuppressive drugs...), pregnancy or breastfeeding status; history of side-effects related to the use of corticosteroids (skin atrophy, vasodilation, hirsutism); allergy to study drugs (either betamethasone dipropionate 0.05% or cefuroxime); not adherence to treatment protocol (one patient in group 1 and five patients in group 2). Therefore, 36 patients in group 1 and 32 patients in group 2 gave the final data for analysis.

Isolation of S. aureus and identification of staphylococcal superantigens: S. aureus was cultured and identified from new skin lesions in AD patients and skin area around the nostrils in healthy subjects. Staphylococcal superantigens were tested by multiplex PCR (Polymerase Chain Reaction). Antimicrobial susceptibility tests were performed using the broth microdilution method for antibiotics: cefuroxime, ampicillin, ciprofloxacin, doxycycline, erythromycin, linezolid, tetracycline and vancomycin.

Statistics: Data were analysed by the EpiInfo software (version 2002). Qualitative variables were presented as frequency and percentage while quantitative variables as mean and SD. Categorical variables were compared using chi-squared or Fisher's exact test, as appropriate. RR and 95%CI (confidence interval) were also used to measure differences in the relationship of results. One-way ANOVA test was used to compare average scores of clinical symptoms and SCORAD index in two groups at baseline, after 1, 2 weeks of treatment. A p-value < 0.05 was considered to be statistically significant.

Results

A group of 128 AD patients consisted of 58.6% of males and 41.5% of females, mean age: 37.65 ± 14.09. Clinical manifestations (in decreasing order of frequency) included itching (100%), dry skin (78.91%), insomnia (75%), non-specific hand dermatitis (57.81%), cheilitis (47.56%), anterior neck folds (42.18%), white dermographism (40.62%), orbital darkening (26.56%), Dennie Morgan infraorbital folds (21.09%), pityriasis alba (18.75%), keratosis pilaris (18.75%), ichthyosis vulgaris (7.81%), nipple eczema (3.9%).

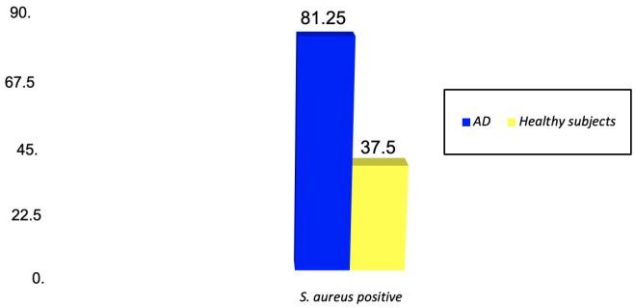

Figure 1: S. aureus was more commonly isolated from skin lesions in AD patients than on the perinotrils of healthy subjects (< 0.001, RR = 2.17, 95% CI 1.44-3.26)

The mean SCORAD score was 12.35 ± 40.55. AD severity was categorised as moderate in 44.53%, severe in 28.12%, and mild in 27.34% of patients. The rates of positive cultures with *S. aureus* in AD patients and healthy subjects were shown in figure 1 and the rates of *S. aureus* strains that secrete superantigens were shown in Figure 2.

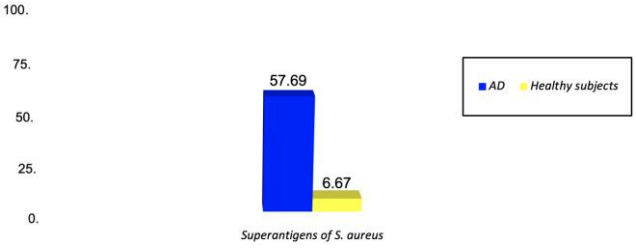

Figure 2: Superantigens were more commonly found from S. aureus strains isolated from AD patients than healthy subjects (p = 0.0006, RR = 8.65, 95% CI 1.29-57.9)

The efficacy of 2 treatment regimens was demonstrated in Table 1.

Table 1: Comparison of the therapeutic effect of the SCORAD index

SCORAD scores (Mean ± SD)	Group 1	Group 2	P values
At baseline	44.61 ± 8.34	43.03 ± 12.98	0.55
At the end of week 1	26.69 ± 6.05	32.53 ± 9.31	
At the end of week 2	16.61 ± 3.85	23.41 ± 7.49	
The difference in SCORAD scores			
Between baseline and end of week 1	-17.92	-10.5	0.003
Between baseline and end of week 2	-28	-19.62	< 0.001

After 2 weeks of treatment, 91.7% of group-1 patients achieved complete *S. aureus* elimination (negative culture) versus only 21.88% of group-2 patients ($p < 0.001$, RR = 5.1, 95% CI 2.57-10.12).

Discussion

Our study confirms that the proportion of *S. aureus* colonisation in AD patients was significantly higher than that in healthy subjects ($p < 0.001$, RR = 2.17, 95% CI 1.44 – 3.26), which is by other studies in the world [2], [3], [7]. In 1997, Goh [9] conducted a similar study on 33 AD patients in Singapore, showing that the rates of positive *S. aureus* detection were 89% in lesion areas, 42% in their healthy skin area, 55% in their outside nostril area, which were considerably higher than those in healthy group (5% in healthy skin area and 35% in outside nostril area).

There were 119 samples positive with *S. aureus*, including 104 samples taken from skin lesions of AD patients and 15 samples from the outside nostril of control subjects. All positive samples were tested by real-time PCR technique to find superantigen-encoding gene segments. Of 104 samples harvested from lesion areas, 60 samples were found to have superantigen-encoding genes, which was equivalent to 57.69%, whereas there was only 1 sample from healthy subjects having evidence of superantigen-encoding genes, which was equivalent to 6.67% ($p = 0.0006$, RR = 8.65; 95%CI 1.29 – 57.9). According to Breuer [9], the proportion of superantigen detection implemented by Latex methodology was 31%. In McFadden's study [10], 65% of *S. aureus* strains isolated from lesion areas of AD patients secrete superantigens.

The treatment efficacy between the two groups was assessed by the SCORAD index. Mean SCORAD scores at baseline were comparable between group 1 and 2 ($p = 0.55$). At the end of week 1, mean SCORAD scores decreased to 26.69 ± 6.05 (difference in-17.92 points) in group 1 and 32.53 ± 9.31 (difference in-10.05 points) in group 2. At the end of week 2, mean SCORAD scores continued to decrease to 16.61 ± 3.85 (difference in -28 points from baseline) in group 1, and 23.41 ± 7.49 (difference in -19.62 points from baseline) in group 2. The extent of SCORAD reduction within each group was statistically significant. SCORAD reduction was significantly greater in group 1 than group 2 either at the end of week 1 or week 2 ($p = 0.003$ and $p < 0.001$, respectively), which indicated that oral antibiotics in combination with topical corticosteroids lead to a higher decrease in SCORAD index compared to merely topical corticosteroids. This finding is in line with Boguniewicz's study [11].

The therapeutic regimen that associates oral antibiotics and topical corticosteroids also had a significantly higher rate of *S. aureus* elimination at the end of treatment (91.7% in group 1 versus 21.88% in group 2, $p < 0.001$, RR = 5.1, 95%CI 2.57 – 10.12). This finding is also in consistency with Weinberg's study [12].

In conclusion, *S. aureus* is the predominant pathogen among patients with AD, colonising much more frequently in AD patients than healthy people. *S.aureus* in AD patients also tends to produce superantigens much more frequently than healthy people. The oral cefuroxime combination with betamethasone dipropionate 0,05% is more efficacious than betamethasone dipropionate 0.05% alone in the treatment of AD patients in the first two weeks.

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