Is Itch Intensity in Atopic Dermatitis Associated with Skin Colonization by Staphylococcus aureus?

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Abstract

Background: Atopic dermatitis (AD) is a highly pruritic skin condition of unclear pathogenesis. Patients with AD are predisposed to colonization by Staphylococcus aureus due to deficiencies in the mechanical and immunological functions of the skin barrier. Recent studies indirectly show that S. aureus may aggravate disease flares in AD. Aims: The aim was to assess the relationship between S. aureus skin colonization and itch intensity in patients with AD. Materials and Methods: The SCORAD index components reflecting itch intensity (excoriations, subjective evaluation of pruritus, and sleep loss) were assessed in 33 adult patients with AD. Swabs were taken from lesional and nonlesional skin. The prevalence and abundance of S. aureus were assessed. Statistical analysis was performed to correlate the microbiological results with the clinical parameters. The control group consisted of 36 healthy volunteers. Results: Lesional and nonlesional skin showed a high frequency of S. aureus colonization when compared with controls (81.8% and 57.6% vs 5.6%, respectively, \( P < 0.0001 \)). The mean concentration (points) of S. aureus was \( 2.01 \pm 1.25, 1.06 \pm 1.14 \), and \( 0.11 \pm 0.46 \), respectively (\( P < 0.0001 \)). S. aureus abundance on lesional/nonlesional skin positively correlated with excoriations and sleep loss (\( \rho = 0.69, P < 0.00001; \rho = 0.44, P < 0.01; \rho = 0.41, P < 0.02; \) and \( \rho = 0.34, P < 0.05 \), respectively). The mean values of excoriations were higher in patients colonized by S. aureus than in patients without S. aureus carriage. Conclusion: S. aureus skin colonization may be one of the factors aggravating itch in AD. It may be hypothesized that restoring the natural composition of the skin microbiome may reduce pruritus intensity.

Key Words: Atopic dermatitis, itch, Staphylococcus aureus

Introduction

Atopic dermatitis (AD) is a chronic skin condition presenting with eczematous lesions and accompanied by intense pruritus. Itch is a major diagnostic criterion of AD and it poses a primary therapeutic challenge in this disease. Pruritus can be mediated by histaminergic and non-histaminergic pathways, but its pathogenesis in AD remains unexplained.

Although histamine was initially thought to be the most important itch mediator, its role in AD is limited. Other itch mediators include 5-hydroxytryptamine, bradykinin, substance P, and various interleukins, such as IL-4, IL-6, and IL-31. IL-31, a Th2-dependent molecule, is especially important in AD. Its upregulation is observed in the atopic skin, and it is considered as one of the most important targets for biological treatment in the future.

Genetically conditioned epithelial barrier dysfunction and imbalance in the profile of the immunological response in patients with AD facilitate colonization by different skin pathogens, including Staphylococcus aureus. IL-31 can be upregulated by S. aureus antigens which implies that this pathogen can aggravate not only disease flares but also the itch in AD.

The aim of this study was to assess the relationship between S. aureus skin colonization and itch intensity in patients with AD.

Materials and Methods

Thirty-three Polish adult patients with active AD were enrolled in the study. The patients’ characteristics...
are presented in Table 1. The diagnosis was confirmed based on Hanifin and Rajka criteria. The exclusion criteria were the following: other dermatoses, clinical signs of skin infection, immunosuppression (either iatrogenic or intrinsic), heart, renal and hepatic failure, diabetes, diagnosis of cancer, and lack of consent. Daily administration of emollients without the addition of potentially bactericidal and/or bacteriostatic agents and of oral antihistamines was accepted. Topical steroids and calcineurin inhibitors were discontinued 5 days before the evaluation. The control group consisted of 36 healthy volunteers sex- and age-matched. The study was approved by the Ethics Board of the Medical University of Warsaw. All participants gave their informed consent before inclusion in the study.

The SCORAD index components reflecting itch intensity, that is, excoriations (0–3 points), subjective evaluation of pruritus (1–10 points), and sleep loss (0–10 points) were assessed. Every patient had a swab taken from a skin lesion and nonlesional skin (volar forearm, if noninvolved). The same investigator (LB) was responsible for the clinical assessment of patients and swab collection.

The swabs used for collecting the biological material were cotton-wool tipped. The transport medium was Stuart (MedLab). Before taking a sample, each swab was wet in 0.85% NaCl solution (BioMerieux). To take the skin swabs, an area of 4 cm² was rubbed for 5 seconds. The swabs were plated on Petri dishes with manniit-salt agar. The incubation for up to 40 hours was carried out in aerobic conditions at 37°C. Based on distinct morphology, obtained colonies were isolated for identification with Vitek MS-DS mass spectrometer. Colonies of the identified S. aureus strains were counted in the cultures to semi-quantify the concentration of S. aureus in the investigated niches. The number of bacterial colony forming units (CFU) was determined based on the correlation with the number of colonies of S. aureus present in the culture and assigned a score on a 0 to 3 point scale (0 pts – no growth, 1 point – up to 10 colonies, 10⁰ CFU; 2 points – up to 100 colonies, 10¹ CFU; 3 points – over 100 colonies, 10² CFU and above).

The results were statistically analyzed to correlate the microbiological analysis with the obtained clinical parameters. The frequency table method was used to describe qualitative variables, and a typical measure of position (mean, median) and variability (standard deviation) were used to describe quantitative variables. For selected pairs of variables, associations/correlations were examined. The Chi-square test (with the Yates correction for small groups (n < 5)) was used to test the relationships between categorical variables. In cases when the number of observations was lower than 50, Fisher’s test was applied. To compare two groups, Wilcoxon rank sum test with continuity correction was used, except attributes with a normal distribution, where the Welch two-sample t-test was applied. Spearman’s rank correlation method was used to measure the degree of the relationship between quantitative and other variables, except the case of normal distribution, where Pearson’s correlation was applied. To identify normal distribution, Shapiro–Wilk normality test was used. The standard level of P value threshold was assumed as P < 0.05.

Results

S. aureus was isolated in 81.8% (27/33) and 57.6% (19/33) of samples from lesional skin and nonlesional skin, respectively (P < 0.04). The control group was colonized in 5.6% (2/36) (P < 0.0001).

The mean S. aureus concentration on lesional, nonlesional, and control group skin was 2.01 ± 1.25, 1.06 ± 1.14, and 0.11 ± 0.49, respectively. All differences were statistically significant (P < 0.001).

S. aureus concentration on lesional and nonlesional skin positively correlated with excoriations (rho = 0.69, P < 0.0001 and rho = 0.44, P < 0.02, respectively) [Figure 1a and c] and sleep loss (rho = 0.41, P < 0.02 and rho = 0.34, P < 0.05, respectively) [Figure 1b and d]. Compared with the patients without S. aureus carriage, the carriers of S. aureus on lesional skin had significantly higher mean values of excoriations (1.54 ± 0.81 vs 0.29 ± 0.49, P < 0.001) and sleep loss (4.65 ± 3.71 vs 1.43 ± 1.99, P < 0.05). Patient-reported itch intensity was also higher in the carriers, but the difference was not statistically significant (data not shown).

Patients colonized by S. aureus on nonlesional skin had higher mean values of excoriations (1.58 ± 0.90 vs 0.88 ± 0.77, P < 0.029) than noncolonized individuals. The mean values of declared itch intensity and sleep loss were higher in the colonized patients, but the difference was not statistically significant (data not shown).

Discussion

The study confirmed the observations of other authors that S. aureus colonization of lesional and

| Table 1: Clinical characteristics of the study group |
|-----------------------------------------------|
| Variable                                     | Value                  |
| Constitutional parameters                    |                        |
| Women/men                                    | 14/19 (42.4%/57.6%)    |
| Age (years)                                  | Range 18-68; mean 31.4±11.9 |
| SCORAD index components reflecting itch intensity (points) |                     |
| Excoriations                                 | Range 0-3, mean 1.27±0.91 |
| Pruritus                                     | Range 1-10, mean 6.27±2.86 |
| Sleeplessness                                | Range 0-10, mean 3.97±3.64 |
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nonlesional skin is a common feature of AD.[11] S. aureus concentration was high in the investigated microniche, which suggested that most patients with AD showed an inability to control S. aureus colonization. This may result from the dysfunctional innate and acquired immune responses as well as epithelial barrier damage.[12] Given the highest abundance of S. aureus on lesional skin in comparison to nonlesional and healthy skin, insufficient physical skin barrier seems to play the most important role in S. aureus colonization.

Kong et al. have shown that S. aureus dominates the microbiome of skin lesions and its abundance in this location correlates with disease severity.[8] The increase in S. aureus concentration precedes AD flares, which suggests that it may be a triggering factor for relapses. It has been shown that many molecules produced by S. aureus act as proteases, superantigens, and facilitators of viral infections and keratinocyte apoptosis.[13] Clinically, these virulence factors have the potential to increase skin inflammation, which is associated with the intensification of pruritus.

The assessment of pruritus intensity in AD is difficult and the evaluation of excoriations seems to be the most objective tool. The study results showed a positive, statistically significant correlation between S. aureus abundance on lesional and nonlesional skin and excoriations. This suggests that an increased exposition to the virulence factors of S. aureus is strictly associated with the sensation of pruritus and scratching. In addition, in the binary analysis, the mean values of excoriations were higher in patients colonized by S. aureus than in patients without S. aureus carriage.

The subjective evaluation of sleep loss and pruritus was less strictly associated with S. aureus colonization in this study. A statistically significant correlation between sleep loss and S. aureus abundance on lesional and nonlesional skin was observed. However, the mean values of sleep loss were significantly higher only in patients with S. aureus colonization on lesional skin when compared with the noncarriers. There was no statistically significant association between itch severity reported by patients and S. aureus colonization on both lesional and nonlesional skin. Nevertheless, it must be pointed out that patients with AD experience itch and sleep loss in a highly individual manner. Furthermore, SCORAD analysis of the subjective symptoms refers only to the past 3 days, while excoriations are more objective and long-lasting signs of pruritus. In future studies, the effort should be made to precisely evaluate excoriations...
and perhaps identify other objective itch determinants. It could also be advisable to use scales designed to assess itch intensity more accurately. One of the tools recently validated in different languages is the ItchYQoL which can be used in clinical trials.\(^{[14]}\)

Although itch pathogenesis is complex, some of its mediators have been identified and their levels can be influenced by \textit{S. aureus}. Hodille \textit{et al.}\(^{[15]}\) have shown that delta-hemolysin and phenol-soluble modulins produced by \textit{S. aureus}, induced degranulation of human mast cells in a dose-dependent manner. Itch in AD is not directly associated with the histamine pathway, but these results suggest that the overabundance of \textit{S. aureus} may contribute to the intensity of pruritus through this mechanism.

Recent studies have described the role of IL-31 in the itch pathogenesis.\(^{[19]}\) IL-31 has been proved to cause symptoms of dermatitis and to aggravate pruritus in animal models.\(^{[17]}\) Overexpression of IL-31 has been reported in the skin of subjects with AD and prurigo nodularis.\(^{[9]}\) This molecule is mainly produced by Th2 cells previously stimulated by IL-4.\(^{[18]}\) IL-31 is bound by receptors present on the surface of keratinocytes, eosinophils, and neurons of smaller diameter.\(^{[19]}\) The exact mechanism through which IL-31 causes the sensation of pruritus is not understood yet.

The antigens of \textit{S. aureus} have been reported to induce IL-31 \textit{in vivo} and \textit{in vitro} in individuals with AD.\(^{[6]}\) Whether this is secondary to the hyperstimulation of the Th2-type response or other mechanisms is not certain. Importantly, the strong sensation of pruritus mediated by IL-31 provokes scratching and skin barrier damage. It has been proposed that the adherence of \textit{S. aureus} to the skin of patients with AD is facilitated due to the impairment of the epithelial barrier and altered exposition of natural moisturizing factor and filaggrin. Defective corneocytes are easily bound by clumping factor B of \textit{S. aureus}.\(^{[20]}\) It is highly possible that the ability of \textit{S. aureus} to adhere to the damaged skin surface results in a vicious cycle: skin colonization, exposition to the virulence factors with secondary upregulation of itch mediators, scratching, and further destruction of the epithelial barrier.

Scratching may also lead to dissemination of \textit{S. aureus} and other pathogens between different niches. This is especially important in the context of frequently observed bacterial and viral skin infections in AD.

Based on the results of the present and above-mentioned studies, the authors propose that microbial dysbiosis should be treated and prevented in AD to reduce pruritus. Patients with AD are advised to use special clothing containing silver ions and bathe regularly with fragrance-free detergents.\(^{[21]}\) Recently, bleach baths have been reported to alleviate AD symptoms, reduce \textit{S. aureus} colonization in children, and be a potential treatment in patients who have undergone more than one therapy with systemic antibiotics during AD flares.\(^{[22,23]}\) Another alternative is to add small amounts of potassium permanganate to the bathing water.\(^{[24]}\) In the future, preparations including probiotics, synthetic AMPs, and other novel antimicrobial agents may prove successful in controlling \textit{S. aureus} colonization in AD without causing significant bacterial resistance and side effects.\(^{[29,29]}\)

Although the study group was small, it seems evident that the \textit{S. aureus} colonization is associated with itch severity in AD. These results should be verified in the trials with larger study groups. Furthermore, at the time of data collection, there were no validated itch assessment scales available in Polish; the determination of itch severity was only based on the SCORAD index.

In conclusion, \textit{S. aureus} colonization of the skin lesions and nonlesional skin is associated with higher values of itch determinants in AD. \textit{S. aureus} seems to cause hyperstimulation of the immune system and overexpression of itch mediators. Prevention and therapy of microbiome dysbiosis could help alleviate itch related to AD.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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