Challenging a paradigm: skin sensitivity to sodium lauryl sulfate is independent of atopic diathesis*

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Summary

Background Sodium lauryl sulfate (SLS) is the best-studied detergent in irritant contact dermatitis. In atopic dermatitis, the two major pathophysiological abnormalities concern skin barrier function and regulation of cutaneous immune responses. The probability of atopic skin diathesis can be assessed by comprehensive analysis of patient history, as well as clinical and laboratory findings, resulting in the Erlangen Atopy Score (EAS).

Objectives To investigate the impacts of (i) atopic skin diathesis according to the EAS and (ii) the physician-assessed diagnoses 'atopic dermatitis', 'allergic rhinitis' and 'allergic asthma' on SLS skin reactions.

Methods This is a retrospective analysis of data from 2030 consecutive patients patch tested with SLS (0-25% aqueous) from two tertiary referral centres in Germany, from 2008 to 2014.

Results Patients with a high probability of atopic skin diathesis showed no significant increase in positive SLS reactions compared with patients without atopic skin diathesis (14-2% vs. 16-8%). The grading of positive SLS skin reactions (1–4) revealed no differences in patients with or without atopic skin diathesis. Furthermore, diagnoses of atopic dermatitis, allergic rhinitis or allergic asthma had no impact on positive SLS skin reactions in multivariate logistic regression analysis.

Conclusions We found no association of increased reactivity to SLS patch tests in individuals with atopic skin diathesis, atopic dermatitis, allergic rhinitis or allergic asthma in a large patient cohort. It therefore seems that the test of skin irritability with SLS, which is currently common practice in many centres, does not allow prediction of susceptibility to irritant eczematous inflammation in atopic vs. nonatopic individuals.

What’s already known about this topic?

- Irritant contact dermatitis and atopic skin diathesis share impaired skin barrier function as a pathophysiological pattern.
- Sodium lauryl sulfate (SLS) is tested at 0-25% aqueous as an irritant control in patch testing, and hence the results might be affected by atopic skin diathesis.

What does this study add?

- Challenging a long-standing paradigm, we found no association of increased reactivity to SLS patch tests in individuals with atopic skin diathesis, atopic dermatitis, allergic rhinitis or allergic asthma in a large patient cohort.
- Thus, irritant control testing with SLS, which is useful in interpreting doubtful allergen patch test results, does not depend on individual atopy status.
The skin barrier is a fascinating but complex interplay of cells, intercellular components and soluble agents. It is formed by corneocytes, corneodesmosomes, corneocyte-envelope-bound ceramides producing the cornified envelope, bound water and lipids. Impairment of the skin barrier is a major pathophysiological hallmark in atopic dermatitis (AD), besides several other skin diseases, and also in allergic rhinitis, allergic asthma and food allergies.

The best known genetic factor in AD is a loss-of-function mutation in the filaggrin gene (FLG), which is found in approximately 10–20% of atopic individuals. In addition, the loss-of-function mutation in FLG was associated with atopy and increased susceptibility to chronic irritant contact dermatitis in a case–control study. However, as most patients with AD do not harbour a FLG mutation, and even 60% of carriers do not develop any skin disease, FLG mutation is an important risk factor, but neither sufficient nor necessary to result in manifestation of AD. The skin of heterozygous carriers is in many ways fundamentally different from normal skin, showing xerosis, scales, keratosis pilaris and palmar hyperlinearity, which are characteristics of ichthyosis vulgaris. Other factors modulating the skin barrier, including environmental influences such as urban life, diet ("fast food") and obesity, were found to be just as relevant.

Besides the impaired skin barrier, the second hallmark of AD is cutaneous inflammation, which is present even in uninvolved skin of atopic individuals. Both AD hallmarks – barrier dysfunction and inflammation – are closely linked and mutually reinforcing. The increased inflammation process negatively affects the differentiation of keratinocytes and decreases the tight-junction proteins. Patients with AD and even with atopic diathesis display skin barrier disruptions, which resemble the effects of sodium lauryl sulfate (SLS) exposure in higher concentrations.

SLS is a detergent commonly used in cosmetics, toothpastes and soaps due to its cleansing properties as an anionic surfactant. In dermatological research, SLS has been widely used to study irritant contact dermatitis. Pioneering works on irritant skin reactions and differences between various chemicals, and between sexes and other cofactors date back to the 1970s and early 1980s. Although several studies have addressed the impact of SLS on many known skin parameters such as natural moisturizing factor, keratin filaments, corneocyte morphology, immune cell invasion and cytokine profiles, the pathophysiology of SLS-induced skin reactions is not yet fully understood.

Sophisticated experimental studies elucidated how SLS may destabilize the integrity of the skin barrier, for example by increasing the pH of the stratum corneum, denaturing keratins, degrading lipid-processing enzymes and lowering expression of serine proteases, thus eventually impairing keratinocyte differentiation. Thus, besides the amount of percutaneous penetration of irritants, complex biological responses are involved in SLS-induced skin reactions. Although the contact time, concentration and vehicle of the SLS application impact on the skin reaction, most studies showed significant variation in these parameters. Furthermore, most studies were conducted with SLS concentrations ranging from 0.5% to 1.0%, although these concentrations are used neither in day-to-day detergents nor in medical diagnostics such as patch tests.

Patients with SLS-positive patch tests display increased erythematous patch test reactions to allergens compared with SLS-negative patients. Aiming to improve the specificity of patch tests, SLS was introduced as an irritant control (SLS 0.25% aqueous) into the baseline series in dermatology clinics following the German Contact Dermatitis Research Group (DKG) guidelines. Indeed, data from the Information Network of Departments of Dermatology (IVDK) revealed that patients with positive SLS reactions tend to react with more irritant but not allergic positive patch test reactions to other test substances, which may appear as erythematous or weak (false) positive reactions. SLS patch test reactions have been frequently investigated for confounders by the MOAHLFA index with multivariate analyses (MOAHLFA is an acronym of the seven items: male sex, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis and age ≥ 40 years). Male sex and age ≥ 40 years were identified to increase the risk of positive (irritant) patch test reactions to SLS 0.25% aqueous.

In epicutaneous patch testing, patients with AD are often excluded because of concerns about flare-up reactions or difficulties in interpreting the results. However, many patients with AD need patch testing to diagnose or rule out additional allergic contact dermatitis. Especially atopic patients often have occupational irritative or allergic contact dermatitis. The Erlangen Atopy Score (EAS) was established in the 1990s to estimate the likelihood of atopic skin diathesis. Various items concerning medical history, atopic signs and symptoms, and lab results are included in the EAS, thus exceeding the commonly used criteria by Hanifin and Rajka for diagnosing AD. However, this score exclusively indicates atopic skin diathesis; it does not diagnose active AD. Hence, a low EAS does not necessarily rule out AD.

Interestingly, no different frequencies of SLS reactions in patients with and without a history of AD were found in a large patch test cohort of 26 879 patients. Older studies with small patient samples yielded different results. In further studies with lower patient numbers, no increased skin susceptibility to irritants such as SLS was observed in individuals with allergic asthma, elevated total IgE levels or a history of AD. These findings remain unexplained as penetration of SLS through uninvolved skin of patients with AD was increased compared with normal skin. As the diagnostic criteria of AD were limited to clinical signs and varied significantly between the aforementioned studies, we hypothesized that the extensive EAS may be a more sensitive tool to identify patients at risk for irritant skin reactions by SLS, in total number and in magnitude of the skin reactions.

Patients and methods

This retrospective analysis was based on patient data collected by the IVDK. The IVDK is a network of departments of dermatology...
in Germany, Switzerland and Austria, dedicated to the epidemiology of contact allergy. Its structure and routine operating procedures are described in detail elsewhere. Briefly, patients’ histories and clinical data and the test results of all patients patch tested in the participating centres are recorded in local databases and, after anonymization, transmitted to the IVDK central office at the University of Göttingen twice a year. Data are subjected to standardized quality control, added to the central IVDK database and analysed according to international standards. For correlation of contact dermatitis with atopic diathesis, the EAS is optionally recorded as part of the standardized IVDK patient history in selected clinics. The study cohort in this manuscript comprised 1582 patients consecutively tested in Erlangen, Germany, and 448 patients tested in Marburg, Germany, from August 2008 to December 2014. This retrospective study was reviewed and approved by the local ethics committee at the University Medical Center Göttingen.

The EAS includes 24 criteria in the categories family history for atopy, AD, clinical signs suggestive for atopy, and laboratory tests (Tables S1 and S2; see Supporting Information). This score was proposed in 1991 and is frequently used in atopy studies. Each item is rated from 0–5 to 3 points. If symptoms are unclear or weak, awarding partial points is recommended for some items. The final score results in a value between 0 and 41.5 points (Table S1). Based on this score, atopic skin diathesis can be probable or improbable. Patients with a total score ≤7 have no or are unlikely to have atopic skin disposition and only very rarely develop AD, while patients with a score ≥10 have a distinctive atopic skin disposition and are prone to clinically manifest AD (Table S2). A score of 8–9 points constitutes undetermined atopic skin diathesis. Thus, all patients with a final EAS of 8–9 points were excluded from analyses of EAS subgroups in this manuscript. In addition to EAS, the IVDK collects information on patients’ history regarding physician-diagnosed atopic diseases (allergic rhinitis, allergic asthma, AD), as described previously. These clinics are also members of the DKG, and allergic asthma, AD), as described previously. For correlation of contact dermatitis with atopic diathesis, the EAS is optionally recorded as part of the standardized IVDK patient history in selected clinics. The study cohort in this manuscript comprised 1582 patients consecutively tested in Erlangen, Germany, and 448 patients tested in Marburg, Germany, from August 2008 to December 2014. This retrospective study was reviewed and approved by the local ethics committee at the University Medical Center Göttingen.

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In addition to EAS, the IVDK collects information on patients’ history regarding physician-diagnosed atopic diseases (allergic rhinitis, allergic asthma, AD), as described previously. These clinics are also members of the DKG, and therefore standardized test protocols and procedures are used, following national and international guidelines. Exclusively patients with exposure to SLS 0.25% aqueous for 48 h were included in this study to exclude bias due to different test protocols (exposure of SLS 0.25% aqueous for shorter intervals results in significantly decreased numbers of SLS reactions). SLS reactions were coded according to a modified Tupker scale. The test preparation SLS 0.25% aqueous was purchased from Herma (Reinbek, Germany), and from 2014 onwards from SmartPractice Europe (Reinbek, Germany). Small Finn Chambers on Scanpor were used (SmartPractice Europe, 8-mm inner diameter). Positive SLS reactions were graded into four categories according to erythema, scaling and infiltration from weak (SLS 1) to severe (SLS 4).

Statistics
Data were managed and analysed using the software package SAS, version 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). The
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In addition to the analysis of MOAHFLA items according to high or low probability of atopic skin diathesis, we also investigated the MOAHFLA items of SLS-positive and SLS-negative individuals (Table 3). Among patients reacting to SLS, there were significantly more men and patients aged ≥ 40 years, but significantly fewer patients with occupational dermatitis, hand dermatitis and AD. Some of the items that were not evenly distributed in these subgroups of patients may interact with each other, for instance occupational dermatitis and hand dermatitis. To quantify the independent impact of each of these factors, as well as other important parameters, most prominently the EAS, on SLS reactivity, we performed a multivariate logistic regression analysis (Table 4). Calculations were done with a positive reaction to SLS as the target variable (dependent variable), and an EAS ≥ 10, AD, allergic rhinitis, allergic asthma, and additional important items as explanatory variables (independent variables). It turned out that only male sex (odds ratio 1.55) and age ≥ 40 years (odds ratio 1.85) significantly increased the risk for a positive SLS reaction, while hand dermatitis had a significant ‘protective effect’ (odds ratio 0.58) in this respect. All other investigated items, including EAS ≥ 10 and past or present AD, had no significant influence on SLS reactivity. Additional data analyses (details not shown) revealed that patients with hand dermatitis were significantly more frequently diagnosed with chronic irritant contact dermatitis than the remaining cohort: 158 of 691, 22.9% (95% confidence interval 19.8–26.2%) vs. 59 of 1339, 4.4% (95% confidence interval 3.4–5.6%).

**Discussion**

We analysed patch test results for SLS 0.25% aqueous, the irritant control of the DKG baseline series, in correlation to the EAS, a rather extensive score to rate the probability of atopic skin diathesis. The EAS relies on clinical examination, family history and comprehensive information from the patient’s past medical history, as well as optional laboratory tests assessing the individual’s atopic diathesis. Although the EAS has been evaluated as a probability score for atopic skin diathesis, patients with an individual EAS > 20 usually present with clinically active AD in our experience. Therefore, we hypothesized an increased intensity of SLS reactions in patients with high EAS, which should be a more sensitive and reliable marker for current skin barrier dysfunction than recording the widely used parameter ‘past or present AD’.

The frequency of SLS patch test reactions did not differ significantly in patients with positive atopic skin diathesis (EAS ≥ 10) compared with patients with a low probability of atopic skin diathesis (EAS ≤ 7). Surprisingly, not even the intensity...
of SLS reactions (1–4) was elevated in patients with high EAS. As expected, patients with AD were significantly over-represented in the EAS ≥ 10 cohort (59.3% vs. 7.0%), suggesting a convincing correlation of high EAS with actual skin disease. However, most earlier studies reported that past or present AD in the patients’ history did not correlate with SLS reactions in patch testing.20,25 At the time of patch testing, patients did not necessarily have any AD symptoms. Current patch test guidelines discourage from testing patients with active AD due to potential flare-up reactions of the skin disease and difficulties in obtaining ambiguous patch test results. Furthermore, while these patients may have had eczema at some point in their lives, the pathophysiology of atopy may not have been established conclusively. Therefore, our approach correlating EAS with SLS reactions seemed to be a more sophisticated and detailed method to investigate the effects of atopic skin disease on SLS reactions in a large cohort.

Increased transepidermal water loss (TEWL) after SLS 0–5% aqueous application was reported exclusively in patients with active AD, without visual differences of the SLS reaction.30 While other studies reported increased TEWL levels even in inactive AD,7,10,37 Although these results point towards compromised skin permeability or impairment of skin barrier function, neither atopic skin diathesis nor former or present atopic diseases influenced SLS skin reactions on a qualitative or quantitative level in our study cohort. However, increased permeability is not necessarily associated with a clinical or subclinical correlate of skin inflammation. The loss-of-function mutations of FLG in roughly 20% of patients with AD in Western Europe may explain increased permeability for SLS in patients with a history of AD.4 Thus, our data suggest that SLS skin reactions are largely independent of skin permeability or impairment of skin barrier function.

Besides skin disease, former reports suggested that SLS skin reactions are independent of other atopic diseases such as allergic rhinitis and allergic asthma.20,38 We confirmed this finding in our study cohort, as these items were assessed

Table 2 Total patient population, and subgroups with Erlangen Atopy Score (EAS) ≤ 7 and EAS ≥ 10 analysed using the MOAHLFA index

| Explanatory variable | All patients (n = 2030) | Patients with EAS ≤ 7 (n = 1215) | Patients with EAS ≥ 10 (n = 521) | χ²-test | P-value |
|----------------------|------------------------|---------------------------------|---------------------------------|---------|---------|
|                      | n (%)                  | n (%)                           | n (%)                           |         |         |
| Male                 | 736 (36-3)             | 462 (38-0)                       | 180 (34-5)                      | 0-17    |         |
| Occupational dermatitis | 514 (25-3)            | 261 (21-5)                       | 164 (31-5)                      | < 0-001 |         |
| Atopic dermatitis    | 473 (23-3)             | 85 (7-0)                         | 309 (59-3)                      | < 0-001 |         |
| Hand dermatitis      | 691 (34-0)             | 347 (28-6)                       | 225 (43-2)                      | < 0-001 |         |
| Leg dermatitis       | 134 (6-6)              | 106 (8-7)                        | 12 (2-3)                        | < 0-001 |         |
| Face dermatitis      | 418 (20-6)             | 241 (19-8)                       | 116 (22-3)                      | 0-25    |         |
| Age ≥ 40 years       | 1337 (65-9)            | 867 (71-4)                       | 290 (55-7)                      | < 0-001 |         |

Age ≥ 40 years and leg dermatitis were significantly over-represented in the EAS ≤ 7 cohort. In contrast, under-represented items were occupational dermatitis, hand dermatitis and atopic dermatitis (χ²-test, P < 0-001).

Table 3 Total patient population, and negative (SLS 0) and positive (SLS 1–3) subgroup analysed using the MOAHLFA index

| Explanatory variable | All patients (n = 2030) | SLS 0 (n = 1693) | SLS 1–3 (n = 337) | χ²-test | P-value |
|----------------------|------------------------|-----------------|-----------------|---------|---------|
|                      | n (%)                  | n (%)           | n (%)           |         |         |
| Male                 | 736 (36-3)             | 593 (35-0)      | 143 (42-4)      | 0-01    |         |
| Occupational dermatitis | 514 (25-3)            | 446 (26-3)      | 68 (20-2)       | 0-02    |         |
| Atopic dermatitis    | 473 (23-3)             | 415 (24-5)      | 58 (17-2)       | 0-004   |         |
| Hand dermatitis      | 691 (34-0)             | 603 (35-6)      | 88 (26-1)       | < 0-001 |         |
| Leg dermatitis       | 134 (6-6)              | 107 (6-3)       | 27 (8-0)        | 0-25    |         |
| Face dermatitis      | 418 (20-6)             | 342 (20-2)      | 76 (22-6)       | 0-33    |         |
| Age ≥ 40 years       | 1337 (65-9)            | 1071 (63-3)     | 266 (78-9)      | < 0-001 |         |

Among patients reacting to sodium lauryl sulfate (SLS), there were significantly more men and patients aged ≥ 40 years, but significantly fewer patients with occupational dermatitis, hand dermatitis and atopic dermatitis.

Table 4 Multivariate logistic regression analyses with positive reaction to sodium lauryl sulfate (SLS) (SLS 1–3) as target variable

| Explanatory variable | Odds ratio (profile-likelihood confidence interval) |
|----------------------|--------------------------------------------------|
| Male                 | 1-55 (1-18–2-03)*                                 |
| Occupational dermatitis | 1-03 (0-69–1-53)                                |
| Atopic dermatitis (past or present) | 0-77 (0-51–1-16)                                |
| Hand dermatitis      | 0-58 (0-40–0-83)*                                 |
| Age ≥ 40 years       | 1-85 (1-35–2-57)*                                 |
| Allergic rhinitis    | 0-92 (0-62–1-34)                                 |
| Allergic asthma      | 0-90 (0-51–1-51)                                 |
| Erlangen Atopy Score ≥ 10 | 1-16 (0-79–1-68)                                |
| Test in winter (October to March) | 1-16 (0-90–1-51)                                |

*Male sex and age ≥ 40 years indicate a significantly higher risk of positive SLS reaction, while hand dermatitis indicates a significantly reduced risk of positive SLS reaction.
separately from the EAS in our patients. Unfortunately, we collected no individual information on the different scoring items of the EAS, only the final score. We therefore may have missed individual symptoms or features of the EAS that might indeed be associated with SLS skin reactivity. Furthermore, different irritants, SLS concentrations, durations of exposition or AD criteria may have yielded different results. It is also well recognized that the reproducibility of irritative skin reactions either by serial testing of the same compound or by prediction of an irritant skin reaction to another irritant chemical differs widely.

In summary, atopic skin diathesis per se is no risk factor for an increased frequency or severity of SLS skin reactions, contradicting our initial working hypothesis that patients with atopic diathesis tend to have more frequent and/or more severe SLS skin reactions. This is in line with the findings from a previous study in 205 metalworker trainees, which found by comparison of TEWL values before and after irritation with SLS, dimethylsulfoxide or sodium hydroxide that skin atopy is not associated with increased skin irritability. In another study of patients with inactive AD and controls, repeated application of SLS 0.5% aqueous over 4 days twice daily for 30 min under occlusion resulted in a significant decrease of natural moisturizing factor levels in all individuals, as well as increased skin permeability in all study participants. In contrast, our study cohort tested with SLS 0.25% aqueous for 48 h of uninterrupted exposure displayed positive reactions in 16.6% of our patients only, independently of atopic skin diathesis. Although inclusion of SLS as an irritant control may be helpful for interpretation of patch test results, a convincing pathophysiological explanation for this medically relevant discrimination has yet to be found. It has also been suggested that the interpretation of SLS patch tests is a potential source of error.

Our data confirmed earlier findings showing a significantly increased risk in logistic regression analyses of a positive SLS reaction in men and in patients \( \geq 40 \) years of age. Several other parameters may influence susceptibility to irritation, such as concomitant disease other than atopy, menstrual cycle, ethnicity, application site and climatic conditions. With regards to climatic conditions, we found no difference in SLS testing during the cooler months vs. the warmer months in our logistic regression analysis (SLS testing during October to March vs. April to September).

Our finding of an independent ‘protective effect’ of hand dermatitis on the frequency of SLS-positive patients (odds ratio 0.58, 95% confidence interval 0.40–0.83) was unexpected. Former studies analysing exclusively TEWL after treatment with SLS 0.5% aqueous found increased values in a small cohort of patients with hand dermatitis with active skin disease. Of note, our patients with hand dermatitis were more frequently diagnosed with chronic irritant contact dermatitis than the remaining patient cohort. Hand dermatitis is more often induced or sustained by external, irritant factors, whereas manifestation of eczema at other body sites may rather be caused by intrinsic factors (e.g. stasis dermatitis, seborrheic eczema, nummular eczema, xerotic eczema and AD). In addition, hand dermatitis is the most common manifestation of occupational dermatitis.

Interestingly, occupational dermatitis was determined a risk factor for positive SLS reactions in former studies but not in this cohort. Patients with hand dermatitis work under hand occlusion (gloves) and wet working conditions, with disinfecting agents or skin-barrier-disrupting detergents (nurses, kitchen workers, craftsmen and others). We conclude that the irritant exposure of the hands is the major cause of the disease, but this is not reflected by SLS reactivity as SLS is not primarily a marker for increased skin irritability in general but only a marker for increased susceptibility at the time of patch testing. Although the exact pathophysiology of SLS skin reactions remains unclear and without association to atopic diseases, we speculate that positive SLS reactions may still indicate a rather internal (genetic?) disposition towards other forms of eczema than exclusively externally caused eczema types.

In conclusion, although an impaired skin barrier may lead to elevated absorption of irritants and allergens into the skin, we found no association of increased skin irritability to SLS with atopic skin diathesis, AD, allergic rhinitis or allergic asthma in a large cohort of more than 2000 patients. SLS skin reactions cannot be associated with skin barrier dysfunction or with consistent polarization of the immune system in atopy. Thus, the current assumption of SLS being an irritant compound in general needs to be challenged in further studies. In daily clinical practice, dermatologists should avoid explaining positive SLS reactions as predisposition towards higher skin sensitivity.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Atopy criteria for the Erlangen Atopy Score.

Table S2 Evaluation of atopic skin diathesis based on the Erlangen Atopy Score.

Powerpoint S1 Journal Club Slide Set.