Atopic Dermatitis – Aspects of Defence Defects

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Lena Hagströmer defended her PhD thesis on May 15, 2009, at the Karolinska Institutet, Stockholm. Cecilia Svedman from Malmö was opponent and supervisors were Lennart Emtestam, Miruna Nyrén and Toomas Talme from Karolinska Institutet, Stockholm, Sweden.

Since there are no laboratory markers for atopic dermatitis (AD), diagnosis is based on major and minor clinical criteria. The major characteristics of AD are pruritus, typical morphology and distribution of lesions, chronic relapsing course, and personal and family history of the condition. The pathogenesis of AD is not fully understood, but several immunological aberrations are found, including impaired cellular immunity, elevated serum immunoglobulin E (IgE) and eosinophil levels and IgE-bearing Langerhans' cells. Colonization of the more-or-less chronically inflamed lesions by microbes may contribute to their perpetuation. The chronic inflammation and microbial colonization/infection, in combination with immune impairments, whether primary or due to treatment effects, may lead to proliferative epidermal changes; hence the suspicion of a link with cancer development.

Fig. 1. Lena Hagströmer (*centre*) after defending her PhD thesis, on May 15, 2009, at the Karolinska Institutet, Stockholm. Cecilia Svedman (*opponent, Malmö, right*) and supervisors (*from right to left*) Lennart Emtestam, Miruna Nyrén and Toomas Talme.

In the studied cohort, there was a statically significant 13% overall excess, driven mainly by excesses of brain cancer and lymphoma (1). Risk elevations were also noted for oesophageal and pancreatic cancer. In addition, a two-fold increase in risk for non-melanoma skin cancer 1–35 years after entry was observed among males, but not among females, and only during the first 10 years of follow-up. With only 12 observed non-melanoma skin cancer cases, however, both the overall excess and the gender difference could be a chance finding. Cases of basal cell carcinoma were not included, as their registration began in 2003. Thus, the non-melanoma skin cancer category includes only squamous cell carcinoma. The net effect on overall skin cancer risk is difficult to predict, since the study population is ageing and thus moving slowly from lower to higher absolute risk. The excess of lung, oesophageal and pancreatic cancer is consistent with smoking and alcohol consumption. No data was collected about these habits among our cohort members. Smoking and/or alcohol over-consumption may have contributed to a biased selection into our cohort of hospitalized patients. Most patients with AD are managed on an outpatient basis, and those who are hospitalized may have a less healthy lifestyle (1). Since the cohort has a high proportion of young patients, who are too young to be in the main age range for cancer, and the frequency of most cancer types increases with age, it would be of interest to repeat the follow-up after a longer period of time. The study was performed using the computerized inpatient register data from January 1, 1965 to December 31, 1999. A Danish study on 6,275 hospitalized patients with AD found similar results to ours, regarding risks for all cancer among the 2,030 adults included (standard morbidity ratio (SMR) 1.5 (95% confidence interval (CI): 1.2–1.9). They also showed, among the adult patients, an increased risk of "keratinocyte cancer" (squamous cell cancer and basal cell carcinoma) SMR 2.4 (95% CI: 1.2–5.4). Melanomas were not increased. Comparison with our cohort is somewhat hampered by the fact that basal cell carcinomas were not registered. Synnerstad et al. (2) proposed that patients with AD have a decreased risk of developing malignant melanoma, but this was not the case in our cohort. Examining atopy as a whole, Eriksson et al. (3) showed no association between atopy or allergic symptoms and cancer, based on a study of 13,811 patients who had been skin-prick tested in 1976–1999.

New treatments for AD include one of the latest, calcineurin inhibitors. The topical calcineurin inhibitors tacrolimus and pimecrolimus were approved in the USA for the treatment of AD in 2000 and 2001, respectively. They were approved

in Sweden shortly thereafter. In 2005, the Pediatric Advisory Committee of the US Food and Drug Administration (FDA) implemented a "black box" warning for topical calcineurin inhibitors due to the lack of long-term safety data and the potential risk of development of malignancies. Although elevated cancer risks are suspected after topical treatment with calcineurin inhibitors, they have not yet been proven. Therefore, a repeated large cohort cancer incidence study of hospitalized Swedish patients with AD is in progress.

Moisturizing creams are important for treating and preventing AD. They are also used as an adjuvant to local steroids. There are many different kinds and combinations and a large number of formulations are available. It is therefore necessary to gather scientific evidence in addition to clinical experience in order to increase our understanding of how emollients cause their effects. We focused on functional changes related to addition of urea alone or urea and sodium chloride together by monitoring trans-epidermal water loss (TEWL), capacitance and electrical impedance spectra (4). We measured increased skin capacitance after 7 days, which persisted after 14 days in the case of urea-containing cream without sodium chloride, but use of a combined product led to a reduction on day 14. The increasing capacitance showed no significant correlation with increases in electrical impedance indices. The increases in the former values were present from day 7 to day 14. Magnitude impedance index (MIX) and Imaginary Part Index (IMIX) increased significantly more with cream containing sodium chloride and urea than with cream containing no sodium chloride. In this study, the increase in capacitance after long-term treatment with moisturizers was not accompanied by a simultaneous increase in TEWL, indicating that the skin was not hydrated to the extent that its water permeability was affected. We observed that TEWL is vulnerable to a number of external factors that are difficult to control and also to the psychological status of the study subjects. No cases of irritation, stinging or suspected allergy were reported by the patients. The addition of sodium chloride to the moisturizer does not appear to have any drawbacks for the cosmetics or any adverse effects in the treatment of AD. The impedance indices MIX and IMIX are correlated with the corneometer readings and, by choosing depth number 2, our measurements mainly reflect changes in the stratum corneum. The findings of this study indicate that moisturizer containing both urea and sodium chloride is somewhat more effective than the same moisturizer without sodium chloride, at least concerning the ability to normalize impedance indices of AD skin.

We evaluated the skin of healthy subjects and patients with AD, using an instrument that measured electrical impedance and other non-invasive methods, TEWL and capacitance and studied the effects of an emollient (Proderm, Ponsus Pharma, Stockholm, Sweden) (5). Dry AD skin showed higher TEWL, lower capacitance, and changes in certain impedance indices. Our findings may be due to simultaneous impairment of the mechanism responsible for skin hydration and barrier function with regard to capacitance and TEWL, which would accord with the findings of comparable studies. We found that certain impedance indices were lower in AD skin, as well as in corneometer measurements. This may indicate that the water content in healthy skin is higher than in AD skin. An improvement in the skin condition was reflected by an increase in capacitance and no change in TEWL, i.e. a moisturizing effect without impairment of the skin barrier function. Changes in TEWL can reflect a multitude of factors, including lipid synthesis processing and organization. On the other hand, a decrease is interpreted as a positive effect of the treatment, reflecting improvement in skin barrier function. The results vary and are affected by several factors, such as design, population (especially age), the part of the body, and the study preparation. On the whole this study showed increases in capacitance with few changes in TEWL measurements and normalization of certain impedance indices after treatment, indicating that the foam did moisturize the skin of patients with AD.

The electrical characteristics of human skin are affected by large variations in factors such as hydration, lipid content, number of cell layers in the stratum corneum, size of corneocytes and some properties of deeper skin layers, which may affect the complex nature of the skin barrier. Impedance indices are regarded as reflecting various properties of the skin, although the mechanisms responsible for changes in indices are not understood, and the techniques for assessing skin electrical impedance are under development. New instruments may increase their reliability by using information from the whole impedance spectra in combination with a new microinvasive electrode system.

Better techniques are needed in order to evaluate the effects of different creams and lotions. To achieve more objective methods of investigation, a gradual development is underway, from subjective assessments of the results of treatment towards more specific measuring instruments. The methods for measuring skin electrical impedance are still being developed, and new instruments may increase its accuracy, for example, more effective use of the information inherent in the spectra by the application of sophisticated mathematical tools. In spite of the fact that AD is a chronic disease, better methods for checking and treatment of the negative effects of AD skin will contribute to the preservation of high quality of life. Expectations are therefore high when it comes to the development of new effective preparations and treatments.

The wide variation in the distribution of SSTR between different skin types (6) indicates that somatostatin is an important mediator between the nervous system and skin, and it may be involved in the pathogenesis of inflammatory skin diseases by modifying the keratinocytes, the vascular endothelium and the skin system. However, does somatostatin have the same inhibitory effect in the skin as the calcitonin gene-related peptide (GCPR)? Has this neuropeptide a specific task or is it secreted together with other neuropetides? Is this peptide involved in the inflammatory reactions or/and in pruritus? Further investigations are required to determine whether different neuropeptides have different distribution patterns.

There is increasing interest in both the interaction between components of the nervous system and target cells, and whether the cutaneous immune system and inflammatory skin diseases have neurogenic components. Neuropeptides secreted by nerve fibres and various cutaneous cells can directly modify the functions of keratinocytes, Langerhans' cells, mast cells, dermal microvascular endothelial cells and infiltrating immune cells. Among these neuropeptides, substance P, neurokinin A, calcitonin gene-related peptide, vasoactive intestinal peptide (VIP) and somatostatin effectively modulate skin and immune cell functions, such as cell proliferation, cytokine production or antigen presentation, under physiological or pathophysiological conditions. Expression and regulation of their corresponding receptors, which are expressed on a variety of skin cells, determine the final biological response mediated by these peptides. Therefore, neuropeptides, neuropeptide receptors and neuropeptide-degrading enzymes participate in a complex network that modulates skin inflammation, wound healing and the skin immune system. Pruritus is a major criterion of AD, and the density of the distribution of cutaneous nerve fibres is much greater in subjects with AD than in normal controls. Data suggest that stressful events and local trauma cause the release of neuropeptides, such as substance P, from sensory nerves in the skin, which may initiate the development of psoriasis or AD in predisposed subjects. This view is supported by case reports of psoriasis patients in whom cutaneous nerve damage resulted in clearance of their skin lesion at that site, but in its reappearance after the recovery of cutaneous sensation.

Somatostatin has been used in several open-label trials as infusional therapy for psoriasis. In a double-blind placebo-controlled study of 21 patients, Matt et al. found a significant clinical improvement in 70% of patients assessed after 15 days of somatostatin treatment. Although the test protocols in these trials are not comparable, the compiled data suggest that somatostatin probably improves psoriasis and psoriatic arthritis, but this therapy has several drawbacks. Its duration of action, with a half-life in the circulation of approximately 3 min, requires the use of a continuous intravenous infusion for sustained action. The effect of somatostatin is not selective, with rebound hypersecretion of inhibited hormones, hyperglycaemia and gastrointestinal side-effects. However, new and more SSTR-selective long-acting somatostatin analogues are under development and these may become a therapeutic option for chronic inflammatory diseases.

All five SSTRs are expressed in normal human skin and in the lesional skin of patients with psoriasis and AD (6), which suggests that in these diseases the various receptors operate in concert rather than as individual receptors. The wide variation in the distribution of somatostatin receptors between the different skin types (6) indicates that somatostatin is an important mediator between the nervous system and the skin, which may be involved in the pathogenesis of inflammatory skin diseases by modifying the keratinocytes, the vascular endothelium and the skin's immune system. However, it is also important to point out that, although certain expression patterns of the SSTR are described (4), very little is really known about the functional relevance of the findings. Some other data suggest a SSTR subtype selectivity. For example, it has been reported that SSTR2 and SSTR5 are the subtypes responsible for somatostatin-mediated inhibition of growth hormone from the pituitary, while SSTR5 mainly inhibits insulin secretion from the pancreas. The data from most clinical trials suggest that somatostatin probably has a positive effect on psoriasis and psoriatic arthritis, and somatostatin binds to all five SSTRs. However, a study of the somatostatin analogue octreotide, which has a high affinity for SSTR2 and SSTR5 and a medium affinity for SSTR3, showed no major improvement in patients with psoriasis. The marked dermal microvascular expansion in lesional psoriatic skin suggests that psoriasis is angiogenesis-dependent. Proliferating vessels express SSTR2, whereas non-proliferating vessels do not. Moreover, angiogenesis can be inhibited by somatostatin. Future clinical trials with new somatostatin analogues are required in order to find a possible new approach for treatment of AD and psoriasis.

Improved knowledge of the mechanisms that drive inflammation in AD may lead to a better understanding of this disease and may shed light on the critical role of the epidermal-barrier function and the immune system. Both lead to IgE-mediated sensitization and must be considered as major targets for therapy. Future developments aimed at correcting the molecular defects in the stratum corneum may provide tailor-made opportunities to improve the barrier function. Early treatment and careful management could improve the outcome and quality of life for patients with AD.

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