

Editorial

Hit early and hit hard in atopic dermatitis and not only in asthma

S. Reitamo, A. Remitz, T. Haahtela

Skin and Allergy Hospital, University Central
Hospital, Helsinki, Finland

Dr Sakari Reitamo
Skin and Allergy Hospital
University Central Hospital
P.O. Box 160
00029 HUS
Helsinki
Finland

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The symptoms of atopic dermatitis include itch, dryness of the skin and superficial inflammation. Sixty per cent of children with severe atopic dermatitis also have asthma (1). Atopy is seen as a hereditary tendency to react towards common environmental allergens with immunoglobulin E (IgE)-antibodies. Atopic patients can be sensitized not only to polypeptides such as pollen but also against microbes or even structures of the patients' own skin. Atopic dermatitis/eczema is a syndrome and about half of the patients show an IgE-associated sensitization, i.e. truly atopic disease. In the other half, IgE does not seem to play a central role. Either IgE-associated or non-IgE-associated dermatitis cannot be distinguished from each other by the appearance of the skin, but the IgE-associated dermatitis runs a somewhat more persistent course. As newborn children do not show sensitization, the question arises whether the IgE-response to environmental proteins is only a secondary phenomenon?

Discussion of the aetiology of atopic dermatitis has until recently been dominated by the 'inwards-to-outwards' thinking (2). The pruritic condition of the skin has been thought to be caused by an inflammation of unclear aetiology. This causes scratching and thereby invasion of superficial microbes such as staphylococci into the skin. Recent genetic studies have undermined this theory. Filaggrin is a structural protein of the outer layer of the skin, which forms a major part of the skin barrier. The major function of the barrier is to prevent water loss from the skin and invasion of foreign polypeptides into the deeper layers of the skin. In patients with active dermatitis the mutations of the filaggrin gene confer significant risks of allergic sensitization and allergic rhinitis as well as asthma (3, 4).

Why is the mutation of the filaggrin gene detected only in approximately half of the patients with atopic dermatitis? It seems that active eczema reduces the concentration of the filaggrin protein in the skin and thereby causes an impairment of the barrier function even in patients with normal filaggrin genes (5). In addition to filaggrin, other factors have an effect on the skin barrier function, namely the balance and function of various protease enzymes and their inhibitors. Furthermore, lipids such as ceramides seem to behave aberrantly in patients with atopic dermatitis (1, 2).

How does the new knowledge of changes to the skin structure affect present thinking of the aetiology of atopic dermatitis? The dysfunctional barrier function seems to be caused mainly by inherited structural or secondary inflammatory changes in filaggrin protein expression. This emphasizes the importance of both the 'inwards-to-outwards' and 'outwards-to-inwards' mechanisms. The impaired barrier function facilitates entry of environmental allergens, which increases inflammation of the skin and may also increase the risk for respiratory manifestations.

Studies in mice suggest that sensitization of the skin to foreign polypeptides can lead to skin inflammation with features similar to atopic dermatitis with increased serum levels in both total IgE and specific IgE to the polypeptide in question. In addition, these mice show an increased bronchial hypersensitivity to the protein used, and this sensitization has only been possible when skin is used as the primary route (6). Primary sensitization has not been successful via the airways (1, 7).

In the treatment of atopic dermatitis a 'step up' approach is used far too often: patients receive mild

topical corticosteroid courses of variable length and no subsequent maintenance therapy to speak of. This is often repeated for years to treat exacerbations. Instead, atopic dermatitis should be treated efficiently from the beginning to clear the inflammation and restore the barrier function. In small children, the fear of side-effects of corticosteroids leads in practice to insufficient topical treatment. In adults, topical corticosteroids are effective, but instead of keeping long intervals between corticosteroid courses, treatment should be continued for a few times weekly after the acute phase is controlled (8). When corticosteroids are not effective enough or are contraindicated, topical calcineurin inhibitors should be used as initial anti-inflammatory medication followed by a maintenance treatment (9, 10). The new idea is to hit early and hit hard by using more of a 'step down' approach to suppress inflammation as soon as possible. After intensive topical treatment, the dosage and dosing intervals are reduced to the levels that are able to keep control of the disease. Such long-term maintenance treatment with tacrolimus ointment has now received a positive opinion from the

Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for both children (>2 years) and adults (11).

Effective long-term treatment of atopic dermatitis restores the skin barrier function and reduces the load of environmental antigens into the skin which in turn decreases skewing towards T helper (Th) 2 type of inflammation and increases Th type 1 reactivity towards normal (12). This could be the reason why treatment with topical calcineurin inhibitors decreases risk of skin infections and does not seem to increase the risk of skin cancer or lymphoma (1, 13).

Today's effective long-term treatment of atopic dermatitis shows a remarkable similarity to treatment of asthma: tackle the inflammation effectively and reduce the probability of long-term functional disturbances of the airways (14). Improved control of the skin inflammation might also have a positive effect to the airways and the overall atopic status (15). Finnish Allergy Programme 2008–2018 stresses the effective treatment of all atopy including atopic dermatitis (16, 17).

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