

Infections as contributing factors to atopic dermatitis

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The pathogenesis of atopic dermatitis (AD) is poorly understood. There is a hereditary disposition for the disease but expression of the genetic trait seems to be dependent on a multitude of environmental factors. Among these, airborne, contact and food allergens which cause allergic sensitization have attracted special interest, but infectious agents also have been claimed to be able to precipitate AD or to give rise to exacerbations of the disease.

The question of whether infections have a causative role in AD or merely are a consequence of the disease is an intriguing one. It has been reported that the onset of atopy, including AD, is frequently preceded by respiratory viral infections (1), and that bacterial skin infections caused by staphylococci may cause exacerbations of the disease (2). On the other hand, AD is associated with immunological abnormalities that would indeed be likely to predispose for infections. Thus several lines of evidence indicate that patients with AD have defective cell-mediated immunity which is most pronounced during, but not confined to, periods of high disease activity. Examples of types of defective CMI in AD include subnormal T cell numbers (3) imbalance of T cell subpopulations (4, 5), poor response to certain T cell mitogens (3, 6), cutaneous anergy and decreased susceptibility to contact sensitization (7), decreased monocyte and granulocyte chemotaxis (8) and impaired antibody dependent cellular cytotoxicity (9-10), and natural killer cell activity (11). These immunological disturbances would certainly be assumed to render the

patient with AD unusually susceptible to a variety of viral and fungal infections, in particular.

Infections occurring with increased frequency and/or severity in AD

In accordance with the assumption that poor CMI in AD would predispose for increased severity of certain infections it is known that *Herpes simplex* and vaccinia virus infections may be unusually severe in AD patients and, likewise, warts and dermatophytoses have been claimed to occur with increased frequency in these patients (review, 7). However, it is not clear whether the increased severity of these infections is a direct consequence of the defective CMI, since it also is possible that the damaged skin may provide a favorable milieu for the replication of these agents. Similarly, the greatly increased occurrence of *Staph. aureus*, and beta-hemolytic streptococci (2) on the skin of AD patients would be assumed to be secondary to skin damage rather than defective CMI. An association between immunological dysfunction and infections is more likely to exist in the case of EBV-infection which is associated with unusually high antibody titers in AD patients (12, 13). Also the increased incidence of multiple recurrences of cold sores and of *Herpes zoster* (14) would be assumed to be due to defective CMI rather than skin damage, since an overrepresentation of these infections has been observed also in patients without on-going dermatitis.

Possible mechanisms of infection-mediated precipitation or exacerbation of AD

The pathological picture of AD is that of an inflammatory process involving a cellular infiltrate of, in particular, T cells of the helper/inducer phenotype, Langerhans' cells and/or macrophages (15). The mechanisms by which infectious agents might be able to influence AD therefore should be assumed to involve release of inflammatory mediators. In particular, mechanisms leading to release of histamine deserve attention, since the skin in AD contains large amounts of histamine which may provoke itching leading to chronic dermatitis (16, 17). Although immediate hypersensitivity seems to play a role in the pathogenesis of AD, it cannot be excluded that the pathogenic events also included cell-mediated immune reactions (18). In fact, it has recently been suggested that the reaction in AD is caused by a combination of elements of Type I, late-phase and delayed-type hypersensitivity (19).

On the basis of the above, infections could hypothetically exacerbate dermatitis in the following ways:

1. Induction of IgE antibody responses to the infectious agent or other unrelated antigens present in the skin. EB virus which is a polyclonal B cell activator that can induce IgE synthesis might act in this fashion (12). Other examples include *Staph. aureus* which may induce IgE antibodies to itself (20) in addition to other antigens (21). Increased IgE antibody formation may also result from HIV infection. HIV may interfere with IgE regulation by suppressing the synthesis of interferon-gamma, a substance shown to have strong negative influence on IgE formation (22).
2. Preformed or newly formed IgE or IgG antibodies may react with the introduced microbial antigen resulting in inflammatory reactions in the skin. In addition to immediate-type reactions by mast cells bearing IgE antibodies, cytophilic IgE bound to macrophages may mediate release of leukotrienes and arachidonic acid (23, 24). It has been demonstrated that a substantial proportion of macrophages infiltrating into AD skin lesions bear cytophilic IgE (25). Preformed IgG antibodies may provoke a cutaneous inflammatory response by complement-mediated reactions. Furthermore, both IgE-antigen and IgG-antigen immune complexes may cause release of prostaglandins and leukotrienes (23, 26).
3. Itching and scratching of staphylococcal containing lesions may induce an inflammatory response (27). This response may be accentuated by bacterial products such as protein A, which has been found to have direct inflammatory effects on the skin (28).
4. Eosinophils attracted to the site of an immediate-type reaction by histamine and eosinophil chemotactic factor may release toxic substances such as "major basic protein" which has been shown to have cytolytic activity against skin cells (29). Skin biopsies from patients with AD have shown widespread dispersion of major basic protein in the superficial and deep dermis (30).
5. Activation of a cell-mediated immune response against viral or other antigens present on cell surface may bring about a destruction of infected cells by various kinds of cytotoxic cells. The role of interleukins in this process is not fully understood but it should be noted that tumor necrosis factor- α and - β , which both have cytotoxic properties, should be expected to be released during an immune response in the skin. Also the formation of interferon during an infectious process will enhance cytotoxic activities. Finally, the fact that an infectious agent, such as *Herpes simplex* or varicella virus, may bring about cytotoxicity should not be overlooked.
6. An infection may lead indirectly to histamine release via stimulation of the formation of the glycosylation-enhancing factor. In addition to stimulating IgE synthesis, this factor has been shown to induce histamine release.

The above-mentioned mechanisms of action for the exacerbation or precipitation of AD are largely hypothetical; very few of these, mechanisms have actually been demonstrated to be operative *in vivo*. However, a common denominator for several possible mechanisms to be histamine which is seen in large amounts in the blood and skin during exacerbations of AD (17, 32). In addition to eliciting skin reactions, histamine will bring about a multitude of immunological changes which have been associated with AD. It also will cause cAMP-accumulation, leading to increased activity of cAMP-phosphodiesterase, which in turn leads to cellular unresponsiveness to beta-adrenergic stimulants (33).

Evidence for a causal relationship between infections and AD

The evidence that infections may precipitate AD in a genetically predisposed individual is circumstantial. Frick et al. (1) described a number of children who developed different forms of atopy including AD after having viral infections caused by parainfluenza, respiratory syncytial virus and cytomegalovirus. Of particular interest are the findings of Barnetson et al. (34), who reported a case of AD developing soon after the patient had had EBV-induced infectious mononucleosis. In another case report, infectious mononucleosis was followed by eczema herpeticum, thus worsening the pre-existing dermatitis (35). We have been interested in EBV as a potential "flare agent" in AD since this virus evokes a multitude of immunological changes, including polyclonal activation of B cells to produce IgE antibodies (36, 37). Irrespective of age and simultaneous occurrence of respiratory allergy, AD patients were consistently found to have higher EBV-seropositivity rates and antibody titers than nonatopic controls (12, 13). Because of these findings, the association of AD with immunological disturbances and the profound immunological changes associated with EBV-infection, it is tempting to speculate that EBV

may indeed occasionally cause an "allergic breakout" according to the concept of Katz (30).

Exacerbation of atopic disease, including AD has been found in a few adult cases of HIV infection (39) and an increased incidence of AD has been noted in children with AIDS (40).

If EBV and HIV may play a role as an activator of AD, the reverse seems to be true for measles virus. In a study of 5 children with AD and measles, Boner et al. (41) observed temporary clearing of the skin lesions in 4 patients. These findings strengthen the concept of AD being an immunological disease, which can be positively or negatively influenced by viruses that profoundly affect the immune system.

There is only limited support for a causal relationship between infections and initial precipitation of AD. Similarly, there is little evidence for the frequently made claim that infectious agents give rise to exacerbations of the disease. We found a higher incidence of *Herpes zoster* and, in particular, multiple (more than 5 episodes per year) recurrences of cold sores in a study of almost close to 1000 patients with AD (14). The increased number of these infections was particularly evident in patients with ongoing AD but was also noted in patients who had no clinically active disease. Therefore, these findings probably reflected the immunological dysfunction in the patients rather than an indicator that infections played any role in exacerbations of the disease.

No firm evidence has been presented to implicate staphylococci as exacerbating agents in AD. Although there is usually heavy colonization of the skin of AD patients with staphylococci (2, 42, 43), actual infection such as seen in the Hyper-IgE Syndrome is uncommon. However, small superficial pustules caused by staphylococci can be identified in many patients with AD (27). Although such lesions may worsen the dermatitis, they may be purely secondary phenomena without playing any role in exacerbations of the disease. Similarly there is no good evidence that staphylococcal IgE antibodies, although reported

to occur rather frequently in the serum of AD patients, play any causal role in AD (44).

Summary

Certain cutaneous viral infections, such as *Herpes simplex*, vaccinia and varicella infections are known to occasionally run an usually severe course in AD. Patients with AD display increased frequencies of recurrent cold sores and *Herpes zoster* and they also have increased antibody titers to Epstein-Barr virus. Heavy colonization of the skin with staphylococci and streptococci is common.

The findings of increased severity and/or frequencies of these infections in AD may be explained by dysfunctional cell-mediated immunity and by cutaneous changes associated with AD. There is suggestive, but not any firm evidence, that infections play a causal role in the precipitation and exacerbation of AD. Infections are thus, in most cases, probably consequences rather than causes of the disease.

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