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The role of infections in atopic dermatitis

La dermatite atopique et infections

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Abstract

Atopic dermatitis (AD) together with asthma bronchiale and allergic rhinitis belongs to the group of atopic diseases. AD is a chronic relapsing inflammatory skin disease with pruritus as the leading symptom affecting approximately 10–20% of children worldwide. AD usually occurs first during infancy but it can persist or begin even in adulthood. The disease not only affects the quality of life of patients suffering from AD but also represents a major economic burden for society because of its chronic relapsing and hard to manage course. In the past decades much effort has been made in elucidating the pathophysiology of AD in order to gain a better understanding of the cause and course on one hand and to develop new strategies for therapeutical agents on the other hand. It has been shown that bacterial and viral infections play a pivotal role in the aggravation of the course of the diseases and might lead to the development of IgE hyperreactivity in a subgroup of AD patients.

Résumé

La dermatite atopique (DA) est une dermatose chronique, en générale prurigineuse. La DA se manifeste principalement tôt dans la petite enfance et peut perdurer jusqu'à l'âge adulte. Pendant toutes les phases, le prurit est prédominant. On trouve les lésions eczématiformes avec leur distribution typique. Les allergènes, l'humidité, la transpiration et les agents irritants peuvent induire une exacerbation du prurit. Il y a des facteurs de provocation comme l'alimentation, les aéroallergènes et les bactériens. Un phénomène bien connu est la colonisation de la peau des atopiques dans 90 % des cas avec du Staphylocoque doré. Les infections à *S. aureus* sembleraient pouvoir aggraver l'intensité de la maladie par la production d'entérotoxines, comme les entérotoxines A, B, C, D, E, G, et le « Toxic shock syndrom » toxin-1 (TSST-1). Dans quelques sujets atteints de DA, on a pu trouver des IgE spécifiques de ces superantigènes staphylocociques. Ces superantigènes produits par les Staphylocoques dorés pourraient amplifier la réponse inflammatoire. De plus, les IgE spécifiques pourraient contribuer à l'activation des mastocytes cutanés et à la libération d'histamine et d'autres substances vasoactives. Une explication possible pour cette colonisation résiderait dans le manque de la production naturelle de peptides antibactériens de type ß-défensine (immunité innée) chez les sujets atteints de DA. Ce déficit pourrait aussi expliquer le risque de développement de surinfections virales.

Keywords: Atopic dermatitis; Bacterial infections; Superantigens; Viral infections

Mots clés : Dermatite atopique ; Bactérien ; Superantigènes ; Surinfections virales

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1. The role of infections in the pathophysiology of atopic dermatitis

1.1. The role of bacterial infections

Staphylococcus aureus (S. aureus) superantigens are presented as "ordinary" antigens in the peptide-presenting groove of the major histocompatibility complex (MHC) complex to the respective antigen-specific T cell [1]. On the other hand, the intact proteins binding the MHC complex are capable of bridging the MHC complex to all T cells with the same β-chain family, irrespectively of their antigen specificity [2]. Antigen-specific and antigen-unspecific T cell activation mechanisms synergistically lead to proinflammatory signals inside the epidermodermal compartment of the skin immune system, which serve as an adjuvant for the ongoing antigen-presentation processes. AD patients are frequently colonized by *S. aureus* in their nasal vestibulum or the skin and *S. aureus* strains are protent producers of *S. aureus* superantigens. *S. aureus* is found in over 90% of patients with chronic AD skin lesions reaching a density of approximately 1 million per cm^2. Acute exsudative skin lesions can contain over 10 million *S. aureus* organisms per cm^2 and even increased numbers of *S. aureus* have been found on clinically normal skin of AD patients [1,3]. In contrast, only 5% of normal subjects harbor this organism on their skin surface. The reason for increased binding of *S. aureus* to atopic skin is not completely understood. As an important factor, scratching enhances the binding of the bacteria by disturbing the skin barrier and exposing extracellular matrix molecules known to act as adhesin for *S. aureus*, e.g. fibronectin, collagens, fibrinogen, elastin and laminin [4]. In addition, bacterial binding was found to be significantly greater at skin sites with Th2-mediated inflammation. One possible reason for this seems to be that IL-4 enhances the binding to the skin by inducing the synthesis of fibronectin, which is an important *S. aureus* adhesin. It is well accepted that these bacteria are responsible for some flare ups or exacerbation states of AD by the secretion of toxins known to act as superantigens, such as S. enterotoxin-A (SEA), S. enterotoxin B (SEB) and toxic shock syndrome toxin-1 (TSST-1). After superantigenic stimulation, skin homing CLA+ T cells form AD patients undergo a TCR-V beta expansion [5–7]. In some patients specific IgE antibodies directed against the staphylococcal superantigens could be found in the skin, leading to the release of histamine from basophils. Superantigens penetrating the skin barrier induce the production of IL-1, TNF-α and IL-12 by epidermal LC and macrophages which evoke the upregulation of E-selectin on vascular endothelium, leading to the influx of CLA+ Th2 memory cells [8]. Additionally, it has been shown that superantigens reduce the apoptosis of monocytes from AD patients via the stimulation of an elevated GM-CSF production.

Based on these pathopysiological mechanisms, an antibacterial effect of topical treatment forms of AD seems to be necessary to remove the staphylococci as trigger factors of AD from this vicious circle in order to enhance the therapeutical benefit of the patients.

Over 90% of AE patients show an increased colonization of the skin with *S. aureus*. Recently a reduced production of defensins in the skin of AE patients has been demonstrated which might contribute to the strong colonization with *S. aureus*. Defensins are proteins produced by keratinocytes and have high antibiotic properties [9]. The relevance of *S. aureus* is underlined by the observation that in AE patients suffering of secondary infection, a combination therapy consisting of antibiotic agents and topical steroid is superior to monotherapy with steroid alone. Although AE patients show increased numbers of T regulatory cells (Tregs) which are involved in the maintenance of tolerance it has been reported recently that after stimulation with superantigens Tregs lose their immunosuppressive properties resulting in enhancement of T cell activity [10].

Some strains of *S. aureus* are able to produce enterotoxins, e.g. *S. aureus* enterotoxin A–E, G, and TSST-1 which can function as superantigens and some patients with AE develop specific IgE against these superantigens. The stimulation by superantigens can lead to a substantial proliferation of T cells and contribute to the amplification of the inflammatory reaction.

Furthermore, specific IgE binding superantigens on mast cells might lead to the release of histamines in the skin resulting in pruritus. Interestingly, significant degrees of specific IgE against *S. aureus* enterotoxin A–E, G, and TSST-1 could be detected in the serum of patients with typical clinical signs of AE but showing no sensitization to aeroallergens and presenting normal total IgE. This form has been formerly referred to as with intrinsic atopic eczema/dermatitis and its part within the category of atopic diseases remains to elucidated [11]. Nevertheless, this observation underlines the importance of bacterial superantigens in the emergence of AE.

1.2. The role of fungal infections

Pityrosporum ovale (P. ovale) is a lipophilic yeast commonly found to colonize AD skin and is thought to elicit immediate and late-phase reactions in these patients. In over 60% of the AD patients, IgE to *P. ovale* can be detected in the peripheral blood supporting the hypothesis of the importance of this organisms as an allergic trigger factor in AD. Many reports clearly indicate the role of *P. ovale* especially in AD located in the head and neck area. Furthermore, skin prick test to *P. ovale* is positive in a subgroup of AD patients. In in vitro assays, it has been shown that immature DC can take up *P. ovale* via the mannose receptor and might thereby induce sensitization against *P. ovale* even in the absence of IgE [12].

1.3. The role of viral infections

Patients with atopic dermatitis (AD) display a higher susceptibility to viral infections. The rapid spreading of *Herpes*