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Atopic Dermatitis: Epidemiology and Pathogenesis Update

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The prevalence of atopic dermatitis (AD) has increased markedly in the United States over the past 5 decades, with current reports varying from 10% to 20% prevalence in US children, and new diagnoses are estimated at almost 11% per year. Recent research in AD pathophysiology and pathogenesis has demonstrated that AD is associated with epidermal barrier dysfunction and that mutations in the filaggrin gene are implicated in barrier defects. These discoveries hold promise for future breakthroughs in the diagnosis and management of AD.

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Worldwide, the prevalence of atopic dermatitis (AD) has increased approximately threefold since the 1960s. In the United States, the reported prevalence of AD currently ranges from 10% to 20% of children. In a recent study of US children 17 years of age or younger derived from National Surgery of Children's Health data from 2003, Shaw and colleagues[1] reported a 10.7% prevalence of new diagnoses of AD or eczema within the previous year. (These prevalence data from the study by Shaw et al are similar to those reported in previous studies involving smaller US populations.[2-4])

Of additional interest are two observations from the study by Shaw et al.[1] One is that the prevalence rates ranged from 8.7% to 18.1% from state to state, with a higher prevalence along the East coast states and in Nevada, Utah, and Idaho. The other observation is that significantly higher disease prevalence was associated with metropolitan living ($P = 0.008$), black race ($P = 0.005$), and education levels in the household greater than high school ($P = 0.004$). These data clearly suggest that social or environmental factors can affect

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the expression of AD, although the specific factors have not been identified.

Immunologic and Inflammatory Pathways: Newer Concepts, Emerging Evidence

AD was once thought to be related to keratinocyte dysfunction, but over the past 2 decades, the understanding of AD pathogenesis focused on AD as a disease of immunologic dysregulation. Immunologic studies have demonstrated that even clinically unaffected skin in patients with AD can show mild epidermal hyperplasia and sparse perivascular T-cell infiltrates. Acutely eczematous skin is associated with spongiosis, which is a manifestation of intercellular edema. In addition, androgen-presenting dendritic cells are thought to be of potential importance in immunologic responses that manifest in atopic skin. However, the most recent evolution in understanding AD concerns genetic mutations that cause barrier dysfunction in AD. These developments have called to question the contributors to AD pathogenesis.

These advances in understanding AD pathogenesis occurred following the identification of a set of mutations in the skin that are associated with barrier defects, specifically, mutations in the filaggrin gene (FLG). Interestingly, as early as 1985, Sybert and colleagues[5] had proposed that filaggrin abnormalities were the cause of ichthyosis vulgaris, which is a condition that was known to be present in a subset of patients with AD. However, the significance of this work was not appreciated until the revolution in genetics occurred within the past decade, with the mapping of the human genome and the identification of the FLG. When the work of Sybert's group and others was revisited,[6,7] it became clear that FLG mutations were, in fact, the cause of ichthyosis vulgaris. (For a comprehensive commentary on this breakthrough, Segre's article, "Epidermal differentiation complex yields a secret: Mutations in the cornification protein filaggrin underlie ichthyosis vulgaris," is recommended.[8])

To review briefly, the stratum corneum layer, also referred to as the epidermal skin barrier, has several major functions, including the prevention of invasion of the body by environmental pathogens and the control of water loss across the epidermis (ie, transepidermal water loss [TEWL]). The stratum corneum consists of between 10 and 30 layers (depending on anatomic site) of keratinocytes that have differentiated to become anucleated corneocytes; in these cells, the plasma membrane is replaced by a layer of large protein molecules—the cornified envelope. Filaggrin, an essential structural protein in the cornified envelope, is expressed first as profilaggrin, which plays an important role in "packing" the keratinocytes into the stratum corneum.

In addition to its contribution to creating a mortarlike, impermeable structure, filaggrin is also broken down, through proteolysis, into humectants—hygroscopic amino acids referred to as natural moisturizing factor. Filaggrin deficiency can adversely affect these functions, impairing stratum corneum adhesion, enhancing TEWL, and causing dysregulation of the skin pH resulting in increased skin permeability.[9]

Loss-of-function mutations in the FLG are quite common: 10% of individuals of European ancestry carry such mutations, which are associated with a reduction of about 50% in filaggrin protein production.[7] Clinically, loss-of-function mutations have been associated with the development of AD.[7,10] In addition, patients who have AD and the FLG mutation also have a greater tendency than do those without the mutation to have more severe or persistent AD,[11] an increased risk for acquiring herpesvirus infection (eczema herpeticum),[12] and an increased risk for early sensitization and multiple allergies (including peanut allergy) and asthma.[10,13]

It is now recognized that a variety of cytokines may mediate inflammation in atopic skin. Acute AD may be associated with T-helper type 2 (T_H2) cytokines, including interleukin (IL)-4 and IL-13, which influence immunoglobulin E synthesis and adhesion molecule expression. In addition, IL-31 has been identified as a unique T_H2 cytokine that is associated with the development of dermatitis and pruritus in experimental animals.

Further, recent studies have demonstrated that thymic stromal lymphopoietin (TSLP) may be expressed in keratinocytes, affected by skin barrier defects. TSLP may mediate inflammation of the skin and other organs, including the bronchial tree.[14]

Microbes in AD: Recent Findings

Colonization with *Staphylococcus aureus* is very common in AD, and patients with AD are at increased risk for impetiginized lesions, pustules, and, occasionally, more significant skin or systemic infections.

With the emergence of community epidemics of methicillin-resistant *S. aureus* (MRSA), concern was raised that patients with AD might be particularly susceptible to such infections. However, several studies have found that the actual rates of MRSA infections in patients with AD are not especially high; in fact, compared to clinical infections seen in nonatopic community members, patients with AD more commonly have methicillin-sensitive staphylococcal infections than MRSA.[15,16]

It has also been shown that the cutaneous immune defense is influenced by innate defense proteins in the skin and that a relative deficiency of antimicrobial peptides can be seen in the skin of patients with AD compared to patients with other inflammatory skin diseases. This deficiency may be associated with staphylococcal colonization.[17]

Interestingly, recent studies have shown that there is an interaction between resident commensal microbes on the skin and antimicrobial peptides. In fact, there appears to be a degree of microbial symbiosis with the innate immune system. For example, *Staphylococcus epidermidis* in normal skin causes keratinocytes to produce antimicrobial peptides, and these suppress cytokine release after minor epidermal injury. Thus, *S. epidermidis* contributes as a barrier against coloniza-

tion of pathogenic microbes.[17] This begs the question of how *S. aureus* has developed colonization in AD skin, as well as the possible sequence of events that changes the standard commensal microbes in this patient population.

Conclusion

AD is a common skin disease, and its prevalence continues to increase worldwide. Over the past 2 decades, research regarding the pathogenesis of AD and related conditions has implicated skin barrier dysfunction and, in turn, that mutations in the FLG adversely affect barrier function. The emerging data on fundamental defects in barrier function have raised the question of whether these barrier defects allow secondary changes in immunologic response that mediate the development of both AD and other atopic conditions. This increasing body of knowledge also has fueled interest in whether early interventions could modulate the development of the secondary atopic phenomena.

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