ATOPIC DERMATITIS AND ITS RELATIONSHIP WITH AUTOIMMUNE THYROIDITIS

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Summary

Introduction: *Atopic dermatitis (AD) is a chronic inflammatory skin disorder with a multifactorial etiology involving genetic, immunological, and environmental factors. In recent years, increasing evidence has pointed to an association between AD and autoimmune diseases, particularly autoimmune thyroid disease (ATD).*

Discussion: *The imbalance between Th1 and Th2 immune responses, shared cytokine pathways, and the presence of IgE autoantibodies provide a mechanistic explanation for the overlap between AD and ATD. Clinical studies and metaanalyses have reported a higher prevalence of thyroid autoimmunity among AD patients, especially in children and young adults. This interplay suggests that early atopy may act as a risk factor for later autoimmune diseases, and that AD should be regarded not only as an allergic disorder but also as part of a broader immunological context.*

Conclusions: *A significant correlation exists between AD and ATD, supporting the role of thyroid screening in selected subgroups of patients with atopic dermatitis. Further large-scale studies are warranted to clarify the causal relationship and to develop personalized mana-gement strategies.*

Keywords: *atopic dermatitis, autoimmune thyroiditis, clinical and immunological correlations.*

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Introduction

Atopic dermatitis is a recurrent inflammatory skin condition that primarily affects children, with 60% of cases diagnosed within the first five years of life. However, it can also begin in adulthood and is more common in males. Recently, there has been an increase in the number of patients seeking medical attention for various symptoms of atopic dermatitis. [1]

Certain forms of atopic dermatitis are linked to elevated IgE antibody levels in response to food or environmental antigens, as well as a personal or family history of atopic conditions like allergic rhinitis or asthma. [2] Atopic dermatitis is a complex condition with various causes, including genetics, epigenetics, environment, and diet. It affects the skin barrier, immune responses involving cells, IgE-mediated hyper-

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sensitivity, and environmental influences. Severe cases of atopic dermatitis are associated with loss-of-function mutations in the filaggrin gene, which may lead to increased water loss through the skin, changes in pH levels, and dehydration. [3]

The epidermis serves as the body's primary defense against environmental factors, blocking allergens, toxins, irritants, and microorganisms from entering while also preventing excessive water loss. In atopic dermatitis, a condition marked by compromised epidermal barrier function, there's a decrease in filaggrin production - a key protein aiding keratin filament assembly - and a reduced level of ceramide lipids, crucial for skin hydration and health. [4]

Genetic research has pinpointed the involvement of genes like FLG, which encode structural proteins in the epidermis. Recent studies have broadened our understanding by identifying mutations in genes regulating these proteins' functions, not just those causing structural alterations in the epidermal barrier. [5]

Atopic dermatitis is a complex condition where genes responsible for the immune system play a crucial role. These genes, including those encoding interleukins (such as IL-4 and IL-13) and cytokines (like RANTES-CCL5 and eotaxin-1 produced by the CCL11 gene), are essential for regulating immune responses. Mutations in these genes can lead to an exaggerated reaction by Th2 lymphocytes, contributing to the inflammation seen in atopic dermatitis. [6] These immune system changes are not confined to affected areas but can also affect healthy skin, making it more sensitive to environmental triggers. This heightened sensitivity can worsen symptoms or even trigger flare-ups of atopic dermatitis. Understanding these immune system dynamics is crucial for developing effective treatment strategies for managing this condition. [7]

Additional genetic variations have been identified that might disrupt the skin's natural barrier function, leading to the expression of atopic dermatitis. The imbalance between Th2 and Th1 cytokines observed in atopic dermatitis can disrupt cell-mediated immune responses and trigger IgE-mediated hypersensitivity, both of which seem to contribute to the condition's development. In the pathology of atopic dermatitis, the presence of two characteristic elements holds significant importance: scratch lesions and the accompanying itch. Patients with atopic dermatitis exhibit a distinct susceptibility to colonization or infection by microbial organisms, particularly Staphylococcus aureus, Malassezia spp., and the herpes simplex virus. [8]

The major risk factors involved in the onset of atopic dermatitis include the presence of a family history of atopy and the impairment of the epidermal barrier function, caused by the mentioned genetic mutations. Other risk factors include socioeconomic conditions, excessive hygiene in the first months of life, pollution, climate, diet, hard water, and obesity. [9]

The clinical scenario can vary greatly depending on the patient's age and the progression and severity of the condition. Itchiness and dryness of the skin are common clinical features. Acute eczema is characterized by intensely itchy, red papules and vesicles with unclear borders, often accompanied by exudation and crust formation. Subsequent or chronic lesions typically manifest as red papules without exudation. Over time, chronic lesions may lead to thickening of the skin and the development of fissures. It's not uncommon for patients to have lesions in different stages simultaneously. [10]

In infants, atopic dermatitis typically manifests as red, papular, or papulovesicular lesions on the cheeks, forehead, or scalp, often with significant itching.

In young children, the condition appears as fine, scaly, lichenified lesions on the flexural areas of the upper limbs, face, or neck. In adolescents and adults, it is characterized by scaly lesions with intense itching, usually found in the flexural areas of the arms and legs, as well as the face or neck. [11] The diagnosis is based on clinical features and the Hanifin and Rajka criteria, which require at least 3 out of 4 major criteria and 3 out of 19 minor criteria to be met. [12]

Atopic dermatitis must be differentiated from other conditions such as seborrheic dermatitis in infants and adults, contact dermatitis, nummular eczema, psoriasis, ichthyosis, and scabies. It's crucial to remember that atopic dermatitis often

coexists with other dermatological disorders. Research has also suggested a possible link between atopic dermatitis and T-cell lymphoma. [13] Patients with atopic dermatitis frequently experience a variety of comorbidities, including other atopic conditions (asthma, rhinitis, keratoconjunctivitis, food allergies), ichthyosis, obesity, metabolic syndrome, cardiovascular diseases, microcytic anemia, attention deficit, anxiety, depression, and other autoimmune diseases. [14]

The goal of treatment is to keep the skin hydrated, control itching, use topical anti-inflammatory agents, and treat infections. The choice of treatment depends on the severity of atopic dermatitis and its impact on the patient's and their family's quality of life. Treatment options include:

1. Topical Treatments: Use of emollients, corticosteroids, or topical calcineurin inhibitors.
2. Phototherapy
3. Conventional Systemic Treatments: These are used with caution due to their toxicity and may include cyclosporine, systemic corticosteroids, off-label methotrexate, or off-label azathioprine.
4. Biologic Therapies: Such as dupilumab, tralokinumab, nemolizumab, and lebrikizumab.
5. JAK Inhibitors: Including baricitinib, upadacitinib, and abrocitinib. [15]

The relationship between atopic dermatitis and autoimmune thyroiditis

The recent findings from cohort studies and meta-analyses shed light on the pivotal role of Th2 cells in atopic dermatitis (AD) pathogenesis. Elevated levels of Th2 cytokines, such as IL-4 and IL-13, have been observed in the skin of early lesional AD patients, where they also down-regulate filaggrin expression, a key protein in skin barrier function. While AD has long been associated with atopic conditions, there's a growing recognition of its connection to various non-atopic conditions, including autoimmune disorders mediated by Th1 cells. [16]

These autoimmune conditions, such as autoimmune thyroid disorders, Crohn's disease, ulcerative colitis, coeliac disease, alopecia areata, vitiligo, certain cancers, cardiovascular diseases, infections, and neuropsychiatric disorders, suggest a broader immunological interplay underlying AD. It's proposed that immune dysregulation triggered by infections or exposure to cross-reactive antigens may induce a Th1 response, leading to inflammation and auto-immunity, contributing to the onset or exacerbation of AD. [17]

Moreover, the involvement of IgE-mediated autoimmunity adds another layer to our understanding. Auto-antibodies against self-binding antigens, detected in AD and other conditions like chronic spontaneous urticaria and Grave's disease, highlight the complex interplay between the immune system and inflammatory disorders. [18]

These insights not only deepen our understanding of AD's pathogenesis but also underscore the need to consider both atopic and non-atopic factors in its management. Further research into these immunological mechanisms promises to unveil novel therapeutic avenues for AD and related conditions. [19]

Atopy and autoimmunity are both potential outcomes of immune system dysregulation. The incidence of autoimmune diseases has risen in recent decades, and while their causes are multifaceted, a commonly accepted model suggests that immune dysregulation, triggered by infection or prolonged exposure to certain antigens, initiates a T helper (Th) 1 response. This response then leads to increasing inflammation and the development of autoimmune conditions. [20]

According to the concept of reciprocal counter-regulation between Th1 and Th2 cells, it is predicted that Th1-driven autoimmune diseases and Th2-mediated allergic conditions would typically occur in separate patient populations, with little overlap. [21] This suggests a distinct immunological divide, where individuals may have a predisposition towards one type of immune response or the other, potentially influencing the onset and progression of specific immune-related disorders. [22]

Recent studies have highlighted new lymphocyte subsets, including Th17 cells, as well as soluble factors like IL-9 and regulatory T cells (T reg), as shared elements between atopic and autoimmune conditions. There's evidence suggesting that infantile atopy heightens the likelihood of developing autoimmune disorders, implying shared immune pathways between these conditions. This partially explains the increased prevalence or coexistence of both atopic and autoimmune diseases. [23]

The thyroid gland stands out as the organ most frequently targeted by autoimmune disorders. Autoimmune phenomena, particularly thyroid autoimmunity, have frequently shown links to other autoimmune conditions, like chronic urticaria in both adults and children. [24]

The research proposes that the innate immune system might influence allergic inflammation, with various cell types such as epithelial cells, dendritic cells, natural killer lymphocytes, and mast cells potentially regulating allergic responses. Additionally, there's a suggestion of interaction between Th2-mediated allergies and Th1-mediated inflammation responses. [25]

The adaptive cellular immune response is broadly classified into two polarized directions. Type 1 responses, guided by Th1 CD4+ T cells and characterized by the signature cytokine interferon (IFN)-gamma, are considered protective against intracellular pathogens. However, they have also been implicated in the onset of autoimmune diseases, such as thyroid disease. Several other autoimmune disorders, like rheumatoid arthritis, juvenile rheumatoid arthritis, insulin-dependent diabetes mellitus, and multiple sclerosis, are associated with a Th1 phenotype. [26]

Autoimmune thyroid disease (ATD) is a condition with diverse causes, involving the immune system's attack on thyroid antigens, triggered by both genetic susceptibility and environmental factors. In ATD, the thyroid gland experiences infiltration by T and B cells reacting to thyroid antigens, resulting in the production of thyroid-specific autoantibodies and subsequent dysfunction in thyroid activity. [27]

Several studies have highlighted a genetic predisposition in autoimmune thyroid disease (ATD), indicating a clear hereditary component where thyroid autoimmunity tends to cluster within families. Additionally, chronic autoimmune thyroiditis tends to peak during early to mid-puberty in childhood. [28]

On the other hand, type 2 responses, orchestrated by Th2 CD4+ T cells and characterized by specific cytokines such as interleukin (IL)-4, IL-5, and IL-13, are implicated in the development of allergic diseases. The conventional idea that Th1 and Th2 cells regulate each other suggests that autoimmune diseases driven by Th1 and allergic diseases mediated by Th2 would typically affect different patient groups. [29] However, recent observations have questioned the accuracy of this traditional Th1/Th2 framework, revealing a more nuanced understanding of the immune mechanisms involved in both host defense and the onset of autoimmune and allergic conditions. This updated perspective introduces additional lymphocyte subsets like Th17 T cells, Treg cells, and new soluble factors, providing a fresh lens through which to explore the intersection of autoimmune and allergic disorders. [30]

Mittermann et al. found that many individuals with atopic dermatitis displayed heightened levels of IgE autoantibodies targeting a wide range of human proteins found in various cell and tissue types. Additionally, they noted a connection between the severity of the condition and the levels of these IgE autoantibodies. [31]

Multiple studies have observed a heightened incidence of autoimmune thyroid disease (ATD) in individuals with allergic disorders. For instance, Pedullá et al. demonstrated an increased prevalence of thyroid autoimmunity among children diagnosed with atopic dermatitis (AD), emphasizing a significant correlation between AD and thyroid autoimmunity in pediatric populations. Furthermore, Pedullá et al. revealed that the frequency of thyroid autoimmunity was significantly higher in children with IgE-mediated AD compared to those with non-IgE-mediated AD, suggesting that both atopy and thyroid autoimmunity could stem from immune dysregulation. [32]

Conclusions

In conclusion, there exists a notable correlation between atopic dermatitis (AD) and thyroid dysfunction among adults. Moreover, specific subgroups, such as younger adults and males with AD, may face an elevated risk of developing thyroid disorders. The link between AD and thyroid disease may stem from immune dysregulation and shared cytokine pathways present in both conditions. Further investigation into the association between AD and thyroid disease in large, diverse populations of children and adults is warranted to determine if a causal relationship exists. Such findings would greatly aid in improving the clinical assessment and management of patients in the future.

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Conflict of interest
NONE DECLARED

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