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Atopic dermatitis in childhood and the atopic march

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RESUMO

OBJETIVO

The objective of this review was to contribute to the understanding of the pathophysiology of Atopic Dermatitis (AD) in childhood and its relationship with the development of the “atopic march”.

MÉTODOS

Narrative review study.

RESULTADOS

A complexity of AD endotypes has been discovered, with at least four types of biomarker clusters that can aid in determining the process of AD development. As of the date of this narrative review, there are two main theories explaining its pathophysiology: the “outside-in theory” and the “inside-out theory.” The first theory is based on mutations in the Filaggrin (FLG) gene, which is fundamental in skin formation and the regulation of IgE synthesis through cytokines IL-4, IL-5, and IL-13. The second theory suggests that AD is a consequence of the intense itching experienced by patients.

CONCLUSÕES

(AD) represents a chronic and multifactorial inflammatory skin condition, with higher prevalence during childhood, particularly in children up to seven years old. It has been observed that atopic dermatitis is the initial expression of an intense atopic phenotype in childhood, which may contribute to the development of other atopic diseases such as allergic asthma, allergic rhinitis, and food allergies, a process known as the "atopic march." However, the pathogenesis of AD has not been fully elucidated, highlighting the need for further research in the area.

DESCRITORES

Atopic dermatitis; Allergic asthma; Food allergy; Allergic rhinitis; Atopic march.

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Pathogenesis of AD and Childhood-Related Factors

Also referred to as Atopic Eczema, AD represents a chronic and multifactorial inflammatory skin condition. Additionally, the variety of clinical manifestations of AD presents a significant challenge in precisely defining its prevalence. However, evi-dence suggests that it is one of the most globally prevalent chronic diseases. Initi-ally, it was considered a childhood disease affecting children up to seven years old, with a prevalence of up to 25% in this specific age group. Nevertheless, data indica-te a substantial occurrence of AD in adults, ranging from 7% to 10%[1-3]. Furthermore, AD primarily contributes to the burden of non-fatal diseases associated with skin conditions[4].

AD can manifest at any stage of life, although it has a higher incidence in childhood. It is characterized by recurrent eczematous lesions (poorly defined erythematous patches with exudation, blister formation, and crusting in the initial stages, and scaling, fissuring, and lichenification in the later stages), intense it-ching, and discomfort5. These manifestations can lead to insomnia, decreased self-esteem, and poor performance in school and work, affecting approximately 80% of patients before the age of six6. Additionally, the course of the disease may persist for many years or show a pattern of remission and relapse[5].

Contrary to previous studies that suggested a remission rate of over 50% in affected children, cross-sectional studies show a one-year prevalence of around 10%[2]. Additionally, a meta-analysis covering seven birth cohort studies with up to 26 years of follow-up revealed no significant disparity in the prevalence of AD between childhood and adulthood[3].

In childhood, AD may be associated with food allergies and inhaled aller-gens, often coexisting with allergic rhinitis and asthma in up to one-third of patients[7-9]. Considering that the development of allergies in children with AD appears to be more related to genetics than to environmental factors[10, 11]. On the other hand, the association of AD with non-atopic comorbidities, including mental health disorders (such as attention deficit/hyperactivity disorder, depression, and anxiety) and autoi-mmune or immune-mediated diseases, has also been described in childhood[12, 13].

Regarding the pathophysiology of the disease, theoretical propositions sug-gest two developmental pathways for AD: the "outside-in" theory and the "inside-out" theory. The "outside-in" theory posits that AD originates from mutations in the Filaggrin (FLG) gene, a crucial structural protein in skin formation, and the regula-tion of IgE antibody synthesis mediated by cytokines such as IL-4, IL-5, and IL-13. Collectively, these factors result in a compromised epidermal barrier and elevated IgE production[14, 15], leading to transepidermal water loss and immune system dysre-gulation, promoting the infiltration of pathogens such as *Staphylococcus aureus*[16] and cellular debris, facilitating the establishment of AD.

On the other hand, the "inside-out" theory suggests that AD may develop as a consequence of the intense itching experienced by patients[17]. The itching leads to lesions, which facilitate the entry of cellular debris and pathogens, including *S. aureus*, the primary agent causing skin infections in 90% of patients with AD[17, 18]. Des-pite being one of the most common dermatological conditions, the pathogenesis of AD remains incomplete.

Despite this issue, findings suggest the complexity of AD endotypes, with at least four distinguishable types identified through biomarker clusters. These en-dotypes are succinctly classified as the "skin-homing chemokines/IL-1R1-dominant" cluster, the "Th1/Th2/Th17-dominant" cluster, the "Th2/Th22/chemokine regulated by lung and activation" cluster, and the "Th2/low eosinophil" cluster[19]. Therefore, these findings highlight the need for further research into the intricate interactions between naturally occurring or induced cells and molecules to determine the patho-genesis of AD[20, 21].

In children and adolescents, clinical phenotypes of AD can be categorized by age of onset, resulting in four types: infancy (under 2 years), early childhood (2 to 6 years), late childhood (6 to 12 years), and adolescence (12 to 18 years)[22, 23].

A study that evaluated early immunological changes during the onset of ato-pic dermatitis indicated that healthy newborns and those predisposed to AD had a greater Th2 bias compared to adults, with low Th1 levels and Th1 cells expressing cutaneous lymphocyte antigen (CLA). In the same study, children (<5 years) with moderate to severe AD showed a delayed development of CLA+ Th1 skin-homing cells in peripheral circulation compared to age-matched controls. It was concluded that while both children and adults with AD share Th2 activation, Th1 activation is consistently present in adults[24]. These observations were consistent with the de-monstration that CLA+ Th2 cells are expanded across all age groups, including in-fants[25].

Additionally, epidermal hyperplasia is more pronounced in the lesional skin of children with atopic dermatitis under five years of age compared to adults with atopic dermatitis. Notably, the non-lesional skin of children with atopic dermatitis also shows significant hyperplasia compared to the non-lesional skin of adults[26]. These analyses suggest that the development of atopic dermatitis may begin before the appearance of lesional skin in children predisposed to developing the condition.

A study that assessed peripheral Th cell characteristics in patients with atopic dermatitis, grouped by age from birth to over 18 years, demonstrated that individuals with moderate to severe atopic dermatitis shared the common trait of Th2 and Th22 deviation in the skin compared to age-matched controls[27]. However, the same study identified some differences among age groups with atopic dermatitis. Infants exhibi-ted higher Th17 patterns, while long-term adults showed higher Th1 patterns. This observation reinforces that the development of atopic dermatitis in childhood may differ from that in adults.

From a disruptive research perspective, it has been demonstrated that the re-pertoire of IgG idiotypes obtained from adults with atopic dermatitis can modulate neonatal thymocytes, inducing them to acquire patterns and cellular phenotypes associated with atopic dermatitis. In this context, using an *in vitro* model of neonatal thymocytes cultured in the presence of IgG from adults with moderate to severe ato-pic dermatitis or control IgG (from healthy donors or polyvalent therapeutic IgG), it was shown that IgG from atopic dermatitis could induce CD4+ and CD8+ thymic T cells to produce IL-17 and IL-10[28], Invariant natural killer (iNK) cells to produce IL-4, IL-17, and IL-10[29], Thymic γδ T cells to acquire a secretion profile of IL-22/IL-17 with a skin-homing phenotype[30] Thymic CD4+ T cells to produce IL-22 and express the skin-homing molecule CLA[31]. Together, these analyses enrich the discussion on the pathophysiological origins of AD, suggesting that IgG idiotypes produced by in-dividuals who developed AD may also contribute to the early stages of its development.

Another characteristic observed in children with AD is the significant increase in the prevalence of asthma and food allergies, particularly by the age of six and among children with early phenotypes of AD, especially those with persistent symp-toms[32]. This observation was also highlighted in a study involving children and ado-lescents with AD, which revealed an increased incidence of other allergic comorbi-dities, such as food allergies, allergic rhinitis, asthma, and sensitization to inhalant allergens in early childhood (<2 years old) compared to older children[23]. These re-cent pathophysiological observations pave the way for a different discussion, sug-gesting that the development of AD may contribute to the onset of allergic diseases, which appear to become more frequent with aging. Although a significant proportion of patients with AD may experience complete remission before the age of two, it is estimated that 40% will continue to deal with the disease for an extended period[33], that subset of patients may represent a population at high risk for what is known as the “atopic march”[34].

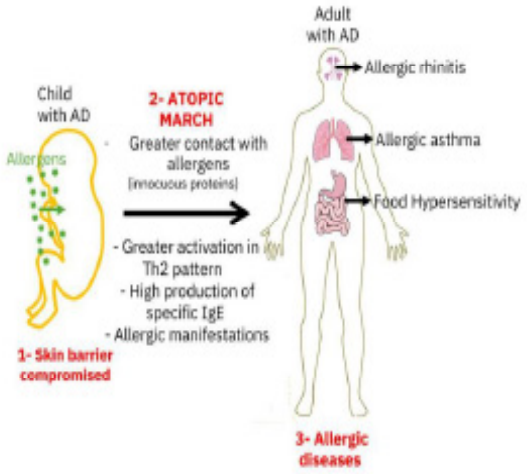
A "atopic march" in patients with AD

Independent of the potential pathogenic mechanisms, patients with AD have a compromised skin barrier that facilitates the transfer of innocuous proteins (inclu-ding allergens) through epithelial barriers. This process promotes systemic sensitiza-tion in a pattern associated with allergic diseases, specifically the Th2 pattern. The establishment of this Th2 pattern, in turn, supports the development of a specific immune response mediated by IgE antibodies. Once established

in epithelial tissu-es, these antibodies mediate the activation of mast cells in an antigen-specific man-ner. Over time, this combination of factors contributes to the progression of what is known as the "Atopic March," where allergic diseases such as allergic asthma, al-lergic rhinitis, and food allergies emerge and persist into adulthood[5, 35, 36].

In the last two decades leading up to this narrative review, the "Atopic March" has been extensively evidenced in the temporal prevalence of allergic diseases in patients with AD, as reported in epidemiological studies[35]. These changes generally begin with AD presenting as food allergies in childhood, which later progress to the development of allergic rhinitis and allergic asthma. This progression can often be observed during childhood[36]. However, these changes certainly result in adults with established allergic diseases (Figure 1), significantly impacting their health by exa-cerbating their sensitivity to environmental allergens, whether ingested or inhaled. These observations have led to the hypothesis that AD represents an early expres-sion of an intense atopic or allergic phenotype during childhood, which could sup-port subsequent epidemiological findings linking it to allergic rhinitis and allergic asthma[37-39].

Figure 1 - Atopic March in Patients with Atopic Dermatitis.



Legend:
1- Patients with AD in childhood have a compromised skin barrier, allowing greater permeability to harmless proteins and facilitating specific immune system sensitiza-tion. 2- During its development, this individual establishes a predominance of Th2-pattern responses with high IgE production, gradually facilitating the development of allergic clinical manifestations. 3- In adulthood, allergic diseases such as asthma, rhinitis, and food allergies become established, characterizing the so-called "Atopic March."

Source: Authors.

Susceptibility to respiratory allergic diseases is significantly higher in children with an early-onset and persistent AD phenotype, characterized by high levels of specific IgE antibodies, progressing in the atopic march towards allergic rhinitis and allergic asthma, compared to individuals who do not produce an intense IgE-mediated response to allergens[33, 40].

Although less than 10% of children with AD progress through the full mani-festations that characterize the atopic march, several studies indicate that individu-als with early-onset AD are more likely to experience symptoms later in life[41, 42]. To-gether, these studies suggest that identifying infants at high risk of AD may enable early interventions to modulate the development of the atopic march. However, to date, no intervention studies aimed at modulating the atopic march have been found in the literature.

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