Atopic March or Atopic Multimorbidity

Subjects: Allergy

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The atopic march encompasses a sequence of allergic conditions, including atopic dermatitis, food allergy, allergic rhinitis, and asthma, that frequently develop in a sequential pattern within the same individual. It was introduced as a conceptual framework aimed at elucidating the developmental trajectory of allergic conditions during childhood. Following the introduction of this concept, it was initially believed that the atopic march represented the sole and definitive trajectory of the development of allergic diseases.

Keywords: atopic march ; atopic dermatitis ; allergic rhinitis ; allergic asthma

1. Introduction

The atopic march is a well-known concept that describes the natural progression of allergic diseases in individuals, particularly during childhood. It refers to the sequential development of different allergic conditions in a predictable pattern within the same person [1]. This concept framework is rooted in insights driven by epidemiological studies [2]. Typically, the atopic march begins with atopic dermatitis (AD) in infancy, followed by the development of allergic asthma and allergic rhinitis as the individual grows older [1].

Atopic dermatitis emerges in 17–24% of children [3]. and 10% of adults worldwide [4]. Among children with mild atopic dermatitis, the prevalence of asthma is approximately 20%, but it escalates to over 60% in those with severe atopic dermatitis [5]. In children diagnosed with asthma (AA), approximately 74–81% also experience allergic rhinitis (AR) [6], and these children typically show signs of allergic rhinitis at an earlier age (2.9 ± 1.7 years) [7].

In the birth cohort study focused on the Multicenter Allergen Study (MAS), Gough et al. have illuminated a noteworthy uptick in the prevalence of AD, asthma, and allergic rhinitis among children with a positive family history of atopy [8]. Similarly, findings from the Dampness in Building and Health (DBH) study by von Kobyletzki et al. have demonstrated that children afflicted with AD exhibit significantly elevated odds ratio (OR) of developing allergic asthma (AA) (OR 3.07; 95% confidence interval (CI) 1.79–5.27) and allergic rhinitis (AR) (adjusted OR 2.63; 1.85–3.73) during follow-up, in contrast to their counterparts without AD [9]. Furthermore, the results of the 2018 Canadian Healthy Infant Longitudinal Development (CHILD) study conducted in Canada have solidified the notion of an augmented risk of AA (absolute risk reduction (aRR), 2.23; 95% CI 1.36–3.67) and AR (aRR 4.44; 95% CI 2.59–7.63) in three-year-old children previously diagnosed with AD [10]. Concurrently, the PASTURE birth cohort study has also brought to light an escalated risk of AA in children by the age of six who had early and persistent AD (adjusted OR 2.87, 95% CI 1.31–6.31) [11]. All these studies, along with numerous others, indicated a propensity for the atopic march, suggesting a natural progression of atopic diseases in individuals [8][9][10][11][12][13][14][15].

The emergence of machine learning has led to a reevaluation of the atopic pattern. [16]. In 2014, Belgrave and colleagues presented findings from two population-based cohort studies that delved into the individual profiles of eczema, wheezing, and rhinitis. Their research also sought to determine if these symptoms adhered to an atopic march pattern in their onset. Their investigations confirmed the heterogeneous nature of developmental profiles for eczema, wheezing, and rhinitis. It was revealed that only a minor fraction of children (7% of those experiencing symptoms) exhibited trajectory profiles that resembled the atopic march [17].

2. Underlying the Atopic March/Atopic Multimorbidity: Patological Mechanism

Considering the various multimorbid disease trajectories explored earlier, it is probable that several unique pathways and mechanisms are at play. Some of these may be shared across all atopic/T helper (TH) 2-dominant diseases, while others could be specific to diseases [18]. How is it that AD contributes to the development of asthma? Many inquiries into the causal relationship labeled as “progression” focus on finding evidence supporting the idea that early childhood AD fosters

the emergence of food allergies (FA) and respiratory allergies. This is believed to occur through systemic sensitization, a consequence of compromised skin barrier function. Consequently, the hypothesis attributing the primary cause of atopic diseases to a deficiency in epithelial barrier integrity is endorsed [19][20].

Skin barrier predominantly depends on stratum corneum. The core of the corneocytes is primarily composed of keratin filaments organized by filaggrin (FLG), a key component that forms a framework for the extracellular lipid matrix [21]. The absence of properly functioning FLG, attributed to FLG gene mutations and the impact of inflammatory and pro-inflammatory mediators affecting FLG expression (acquired deficiency), leads to a disruption in the essential processes required for the stratum corneum's protective role [22]. In particular, the compromised function of the damaged skin barrier facilitates the entry of diverse allergens/haptens, environmental pollutants, and toxins [23]. Functional loss resulting from mutations in FLG, which specifically impact the epidermal barrier, increases the susceptibility to peanut allergy. This association holds true even when accounting for the presence of AD and employing varying levels of stringency in defining peanut allergy [24][25][26]. Notably, a heightened exposure to environmental peanut allergens, coupled with both FLG mutations and the presence of AD, amplifies the risk of developing peanut allergy in an additive manner [27].

Thymic stromal lymphopoietin (TSLP) is a cytokine that belongs to 4-helix bundle cytokine family, primarily targeting dendritic cells. In co-culture, these dendritic cells have the capacity to stimulate the production of IL-4, IL-5, and IL-13 from naive CD4+ T cells [28]. TSLP is naturally expressed at baseline levels in mucosal surfaces such as the gut and lung, as well as in the skin. Moreover, its expression can be heightened in response to exposure to viral, bacterial, or parasitic pathogens, as well as Toll-like receptor (TLR) agonists [29]. Apart from influencing Th2 cell polarization via antigen-presenting cells, TSLP also has a direct impact on CD4+ T cells, CD8+ T cells, and Treg cells [30][31]. TSLP's reach extends to promoting Th2 cytokine responses by affecting mast cells, innate lymphoid cells (ILCs), epithelial cells, macrophages, and basophils. Notably, TSLP plays a significant role in basophil biology; in vitro, it can induce basophil maturation from bone marrow precursors in an IL-3 independent manner [32]. Additionally, basophils elicited by TSLP in vivo exhibit a distinct phenotype compared to those elicited by IL-3 [32][33].

The connection between atopic diseases and TSLP expression was initially established by Soumelis et al., who observed significantly increased expression in the lesion skin of individuals with AD [34]. Subsequent investigations revealed TSLP expression in the airways of asthmatics and the nasal passages of individuals with AR [32][35]. In asthmatic airways, TSLP levels correlated with the expression of Th2-attracting chemokines and the severity of the disease [36].

Children exhibiting compromised anti-viral interferon production face a scenario where virus infected nasal epithelial cells discharge viruses (for example rhinovirus or respiratory syncytial virus) into lower respiratory tract. That induces necrosing cell death that release active interleukin-33, ultimately triggering type 2 inflammation, and wheeze [37]. Additionally, antiviral interferons play a crucial role in directly inhibiting proliferation of Th 2 cells and type 2 innate lymphoid cell, as well as the production of type 2 cytokines, IL-4, IL-13 [38]. One critical factor contributing to compromised antiviral interferon (IFN) production involves the interconnection of IgE molecules present on the surface of plasmacytoid dendritic cells (pDCs). These cells serve as the primary suppliers of IFN-alpha when exposed to viruses [39].

Additional confirmation about IFN role is provided by a study indicating that adults with AD encounter increased occurrences of viral or bacterial infections beyond the skin or at a systemic level [40].

The exposome hypothesis posits that the modern lifestyle's environmental exposure to harmful substances can impact the epithelial barriers of the skin, gastrointestinal tract, and airways. These substances include, but are not limited to, cleaning products, detergents, microplastics, nanoparticles, elevated concentrations of ozone and particulate matter, cigarette smoke, and certain food additives such as enzymes and emulsifiers. Sustained exposure to microplastics at low doses holds the potential to induce dysfunction in the intestinal barrier and cause injury to epithelial cells [41][42]. Findings from a study on human lung epithelial cells indicate that exposure to microplastics, such as inhaled polystyrene, results in inflammatory and oxidative damage. Additionally, it leads to the breakdown of intercellular junction proteins in the lung, contributing to impaired lung barrier function [43].

Individuals with AD commonly experience a reduction in bacterial diversity and an increased prevalence of the pathogenic bacterium S. aureus on their skin. Several factors contribute to this, including elevated skin pH, decreased levels of FLG and its associated breakdown products, and reduced levels of antimicrobial peptides in AD patients. These conditions create a conducive environment for the colonization of *S. aureus* on the skin, potentially triggering cutaneous inflammation and exacerbating AD symptoms through direct proteolytic damage to the epidermal barrier and immune dysregulation [44]. Colonization by S. aureus is linked to the severity and persistence of AD, as well as infectious and atopic comorbidities [45][46][47]. The activation of the immune system by S. aureus is facilitated through the expression of proteases, toxins,

superantigens, and other virulence factors. Consequently, S. aureus skin colonization is hypothesized to coincide with the development of the atopic march. Supporting this, a recent experimental study demonstrated that an enterotoxin-producing S. aureus strain can induce allergen-induced excessive lung inflammation and airway hyperreactivity through an IL-17A-dependent mechanism, while also intensifying type 2 inflammatory responses [48].

Beyond disturbances in skin microbial communities, an increasing body of evidence highlights the significance of gastrointestinal dysbiosis in the initiation of AD and the broader atopic march. The gut microbiota plays a crucial role in influencing and modulating the immune response, thereby influencing susceptibility to immune-mediated disorders, including AD and allergic diseases [49][50].

Marenholz and colleagues conducted a genome-wide association study (GWAS) 2428 cases with AD in infancy and AA in childhood, along with 17,034 controls. Their investigation identified seven susceptible sites linked to the atopic march: FLG [1q21.3], AP5B1/OVOL1 [11q13.1], IL4/KIF3A [5q31.1], IKZF3 [17q21], C11orf30/LRRC329, EFHC1 [6p12.3], and rs99322 [12q21.3] [51]. Additionally, Gupta et al., conducted pathogenic genes: IL4, IL5, TSLP, RNASE3, FOXP3, KCNE4, CD4, IL4R, and CCL26. These genes were identified through large-scale and high-throughput bioinformatics analyses, and their roles in the atopic march await further experimental validation [52].

Epigenetic mechanism plays a role in governing gene expression and can be implicated as a causative factor in diseases. Numerous epigenome-wide studies have uncovered associations between DNA methylation in blood and conditions such as FA and AA [53][54][55].

Peng et al. have conducted DNA methylation analyses on cohorts from the Generation R study and Project Viva. Through meta-analyses they established associations between differential methylation profile in the peripheral blood of mid-childhood children and factors such as food allergens, environmental allergens, and atopic sensitization. Various genes linked to methylation sites were enriched in pathways related to AA, including eosinophil peroxidase, IL-4, IL-5 receptor A and proteoglycan 2. Additionally, the study identified several methylation site sin cord bloods that were correlated with allergic phenotypes in mid-childhood. Notably, some of these cord blood methylation sites persisted into mid-childhood, suggesting a longitudinal time trend [56]. The aforementioned findings imply that epigenetics could play a role in the development of allergic diseases [1].

3. Prevention Strategies for Atopic March/Atopic Multimorbidity Development

Since the compromised skin barrier function is thought to be an initial point of atopic multimorbidity development, one of the principal strategies in prevention is preservation of skin barrier function [57]. The first authors that have shown that regular application of standard emollients decreases skin pH and increases colonization of Streptococcus salivarius are Horimukai and Simpson [58][59]. The Prevention of AD By a Barrier Lipid Equilibrium Strategy (PEBBLES)study revealed that applying a trilipid-rich emollient, predominantly composed of ceramides, topically to high-risk infants from birth until six months of age reduces the likelihood of food sensitization at six to twelve months [60]. Notably, the introduction of the emollient cream within the first three weeks of life showed a significant impact [61]. The effectiveness of emollients in preventing AD has been called into question by two larger studies. One of them is The preventing of AD and Allergies in Children (PreventADALL) in which emollient use after twelve months did not reduce the incidence of AD but has mildly increased the risk of AD (3.1%, 95% CI: 0.3% to 6.5%). Ref. [62] The other study was the Barrier Enhancement for Eczema Prevention (BEEP) trial that followed high risk infants. At the age two years old, there were no significant difference in AD incidence and/or severity [63]. There is still a considerable amount to be clarified concerning the „best practices“ for the use of emollients. It remains uncertain whether emollients actually prevent AD and FA, or if they merely postpone their onset or reduce their severity. Additionally, there has been limited exploration into assessing the varying significance of different ingredients in emollients [64].

Supplementing with probiotics during pregnancy and/or infancy might offer protection against the onset of AD [65][66]. However, there is currently no evidence to support their protective effect against FA or other allergic disorders [67]. There is a lack of adequate evidence supporting the use of other nutritional interventions, including prebiotics, hydrolyzed formulas, or vitamin D supplementation [68].

Numerous randomized controlled trials have demonstrated introducing allergenic foods like peanut or egg to high-risk infants, especially those with severe AD or existing food sensitization, can potentially lower the risk of developing peanut or egg allergies, respectively [69][70][71].

Various primary prevention approaches for asthma and allergic rhinitis have been explored, such as early life house dust mite avoidance and prophylactic sublingual immunotherapy in sensitized children [72]. However, none of these strategies have demonstrated enough evidence to warrant their inclusion in routine clinical practice at present [73].

4. Biomarkers of the Atopic Multimorbidity

Advancements in technology, including transcriptomics, genomics, and proteomics, open new avenues for exploring potential biomarkers of atopic march and atopic multimorbidity [74]. The idea of biomarkers presents a key for future personal and precise treatment. So far, several predictors or biomarkers have been found. The expression of fatty-acid-binding protein 5 (FABP5) in the skin and T cells of individuals with atopic march and in murine models of atopic march showed a positive correlation with IL-17A levels in both the skin and serum. This suggests that FABP5 may play a role in the advancement of the atopic process by fostering Th17 inflammation. Furthermore, FABP5 is proposed as a potential biomarker for atopic march [75]. The variation in the Toll-like receptor 2 genes (TLR2-16934A > T) among individuals with AD and total IgE levels ≥ 106 IU/mL is linked to the presence of asthma, allergic conjunctivitis, or a family history of atopic diseases [76]. The Th17 pathway and the IL-17 cytokine family might play a role in the progression of allergic inflammation, with serum IL-17 levels correlating with the severity of allergic rhinitis in patients. Additionally, the Th17/IL-23 pathway is implicated in the development of asthma. IL-23 levels are significantly elevated in children with AA compared to healthy controls [77][78].

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