

EDITORIAL

Risk factors for atopic dermatitis in infancy: are we closer to effective primary atopy prevention?

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Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder that often presents as the first clinical manifestation of atopy in infancy [1]. In industrialized countries, AD affects up to 20% of infants and is a significant public health burden [2]. In recent years, the prevalence of AD appears to have risen, a phenomenon that has been largely attributed to changes in lifestyle, nutrition and other environmental factors [3, 4]. The pathogenesis of AD is complex and not completely understood [1, 5]. The high prevalence of AD in families with a history of atopy highlights the importance of genetic factors [6]. The development of AD also appears to be strongly influenced by environmental factors [5]. Identifying these risk factors may provide the key to effective public health strategies in preventing atopic disorders [7].

In infancy, AD is closely associated with IgE sensitization to food antigens [5, 8]. Non-IgE-mediated food allergy has been demonstrated in about 10% of infants with AD [9]. Hypoallergenic diets have therefore become one of the mainstays in the long-term treatment of AD in infancy [10, 11]. It is important to understand that sensitization to food proteins is not limited to formula-fed infants. Intact food antigens are secreted into breast milk and may thus reach the intestinal mucosa of the infant [12]. In breastfed infants, allergen restriction can be effectively achieved by a strict maternal elimination diet [12]. However, these diets are not without risks and need to be closely monitored as the energy and micronutrient intake of mother and infant may be compromised [13]. In formula-fed infants, extensively hydrolysed and amino acid-based formulas have proved effective in treating the manifestations of cow milk and other food protein allergies [11, 14]. In older children and adults, food allergy becomes less prevalent [15], whereas inhalant sensitization increases [16]. This shift in sensitization patterns is reflected in the 'atopic march': the resolution of food hypersensitivity and AD in late infancy and early childhood, in exchange for an increase in the prevalence of asthma and allergic rhinitis in older children [17].

The 'hygiene hypothesis' has been used to explain the recent increase in atopic diseases [18]. This theory is based on the observation of an apparent inverse relationship between household size or microbial exposure, and allergic manifestations. On an immunological level, this polarity correlates with two T-helper (Th) cell populations with distinct cytokine profiles, Th1 and Th2 [19]. After birth, a Th2-predominant cytokine profile in response to allergens predominates, suggesting an immaturity of the neonatal immune system in mounting a Th1-type immune response [20]. This model is supported by a recent study demonstrating reduced inter-

leukin-12 production by neonatal antigen-presenting cells in response to allergen stimulation [21]. The lack of microbial antigenic stimulation in Western countries may contribute to the persistence of a Th2-cytokine immune profile and may predispose to the development of allergies [20]. Low socio-economic status, large family size and exposure to the farm environment have been shown to be protective against atopic disorders [18, 22]. However, this dichotomy is not always clear-cut. While respiratory infections may favour a tolerogenic Th1-type response, they may also promote allergic airway disease [23]. Similarly, gastrointestinal infection may induce a Th1-type response but at the same time increase the risk of sensitization to food proteins via impaired mucosal integrity and increased gut permeability [24].

From a public health perspective, it has become a priority to develop effective strategies to prevent the development of atopic disorders in high-risk infants [7]. The promotion of breastfeeding has been one of the key strategies in primary allergy prevention [10, 25]. Breastfeeding is considered the most appropriate form of infant nutrition as it provides a suitable mixture of nutrients, nucleotides, growth factors, lymphocytes, immunoglobulins and several anti-inflammatory and immune-modulating compounds. However, prolonged breastfeeding with its attendant low-dose exposure to secreted food antigens may increase the risk of infantile food hypersensitivity [26]. The question whether breastfeeding can protect from allergies has thus remained an area of debate. Low concentrations of transforming growth factor beta (TGF- β), tumour necrosis factor-alpha (TNF- α) and IgA in human milk are factors associated with the sensitization to food proteins in breastfed infants [14]. The recommendation of exclusive breastfeeding for at least 6 months appears to balance adequately the nutritional and general health benefits of human milk against the risk of food sensitization [25].

The term 'oral tolerance' describes an active immune response that determines how the immune system reacts to luminal food antigens, bacterial pathogens and antigens from commensal gut bacteria. The development of oral tolerance is a complex process [27]. The gut-associated lymphatic tissue (GALT) appears to play a critical role in modulating the development of oral tolerance [28]. Breastfeeding promotes an intestinal milieu rich in *Lactobacilli* and *Bifidobacteria* [29]. These commensal gut bacteria are thought to induce a shift towards a Th1-predominant immune profile [30]. Bacterial products appear to be critical in modulating this immune shift by acting onto innate immune cells, such as dendritic cells or macrophages [31]. Interaction of the intestinal epithelium and immune system via toll-like receptors may be one of the

mechanisms involved in regulating tolerance to dietary and microbial antigens in the gut [32]. Other factors in breast milk may also influence gut integrity and permeability and promote the development of tolerance [33]. Recent studies by Kalliomäki et al. [34] have demonstrated that administration of probiotic lactobacilli during pregnancy and lactation significantly reduces the incidence of AD in young infants. Based on this important observation, it appears likely that microbial and other environmental factors modulate the fetal and neonatal immune responses and influence whether a shift to a Th1-predominant profile takes place [20]. Furthermore, use of antibiotics during pregnancy and early infancy may potentially increase the risk of food sensitization [35].

In the present issue, Kerkhof et al. [36] attempt to identify risk factors for AD during infancy. They studied a cohort of 304 high-risk infants of mothers with asthma or respiratory allergy who had taken part in the *Prevention and Incidence of Asthma and Mite Allergy* (PIAMA) study [37]. Of these, 76 (25%) infants had AD. The cohort was characterized with regard to birth characteristics and environmental factors. Using multiple logistic regression analysis, a birth weight greater than 4000 g and day-care attendance were found to increase the risk of AD significantly, whereas exclusive breastfeeding for at least 3 months appeared to be protective. The study by Kerkhof et al. [36] illustrates some of the difficulties in conducting large-scale epidemiological studies on AD. The increased risk of AD in high birth weight infants only applied to a subgroup of the cohort. Furthermore, infants were not randomly allocated to feeding mode or day care attendance. As the number of study subjects was relatively small, the statistical power was often insufficient for multivariate analysis, and results should therefore be interpreted cautiously.

Future research should focus on primary and secondary prevention of atopy and its manifestations [7]. Based on recent studies, interventions aiming to achieve immune modulation towards a Th1-type immune response *in utero* and during the first months of lactation appear to hold promise. Kerkhof et al. [36] have provided further evidence for a protective role of exclusive breastfeeding against the development of atopy in the first 3 months of life. This protective effect, however, appears to be small [26, 38]. It remains unclear whether the observed slight reduction in the incidence of atopic manifestations was due to direct immune modulation or indirectly mediated via the effects of commensal gut bacteria. Perinatal supplementation of mother and infant with probiotic lactobacilli has been shown to be effective in preventing AD [34], but requires further prospective evaluation.

Large-scale, population-based studies to assess the preventative effects of probiotic bacteria on atopy development in infancy are now called for. These studies need to evaluate carefully the benefits, risks and cost-effectiveness of probiotics and other immune modulators during pregnancy and lactation. Potential long-term adverse effects of overstimulating the immune system of the young infant towards a Th1-predominant response need to be carefully considered. These studies will be critical for the implementation of evidence-based public health strategies for the primary prevention of AD and other atopic disorders in childhood.

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