Chapter

Allergic March

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Abstract

Atopy is an inherited tendency of producing immunoglobulin E on common proteins from the environment like pollen, house mites and food. The presence of atopy represents a risk for the development of allergic diseases like atopic dermatitis, asthma, allergic rhinitis and food allergy, although atopy can also be present only in the form of asymptomatic sensitization. Allergic diseases share common inherited and environmental risk factors, immunologic patterns of allergen-specific Th2 response and efferent phase of immunologic reaction characterized with the production of IgE and activation of granulocytes. The presence of one disease increases the risk for developing other diseases. Allergic diseases demonstrate characteristic sequence of incidence in childhood which is called allergic/atopic march and starts with atopic dermatitis in early infancy. Disrupted integrity of the skin in atopic dermatitis contributes to the development of sensitization and increases the risk for development of other allergic diseases. The discovery of filaggrin gene mutation opens the possibility for causative incidence of allergic diseases and for prevention of development of atopic march. But, the causal link from atopic dermatitis to asthma is still a matter of debate.

Keywords: allergic march, atopy, children

1. Introduction

Allergic diseases are the most common chronic condition in childhood. Epidemiological studies observed increase in the prevalence of allergic diseases from the middle of the twentieth century, which is explained by environment and lifestyle changes and improvements in modern Westernized societies. At the beginning of the twenty-first century, stagnation in the prevalence of asthma while increase in the prevalence of food allergy was noticed, which announced the second wave of allergy epidemics [1–3]. The first atopic phenotype that starts in early infancy is atopic dermatitis (AD). It is estimated that it affects up to 20% of children. Disrupted integrity of the skin barrier contributes to the development of sensitization to food and aeroallergens and also increases the risk for the development of food allergy. It is considered that 30% of children with AD have food allergy, and 30% develop asthma and 75% allergic rhinitis [4]. About 3–5% of children have been diagnosed with food allergy, and up to 50% of them have AD [1]. AD and food allergy can coexist and can also appear independently in infancy and in the first years of life. In the following years, wheezing induced by viruses like respiratory syncytial virus or rhinovirus and sensitization to inhalational allergens can be observed. As the child grows up, respiratory symptoms are more common and occur outside of the infection; introduction of anti-inflammatory drugs is needed, i.e., the signs of asthma occur. Preschool and school age are the time of

appearance of allergic sensitization to pollen of grass, weed and tree pollen, and the beginning of allergic rhinoconjunctivitis which persists in adolescence and the young adult age.

At the same time, remission of atopic dermatitis and food allergy is noticed, while asthma and rhinitis symptoms continue. Sensitizations to pollen and cross-reactions to nuts, fresh fruits and vegetables may induce oral allergy syndrome, the type of food allergy that occurs in the school age. Asthma may disappear in teenage years, but after some period of remission, skin and respiratory symptoms can appear once again. In early adulthood, skin and lung symptoms are related to tobacco smoking, occupational exposures and lifestyle, and they manifest like contact dermatitis or asthma-chronic obstructive pulmonary disease overlap syndrome [5].

Atopic dermatitis, food allergy, asthma and allergic rhinitis in childhood share the common genetic, epigenetic and environmental risk factors, while the underpinning pathogenesis is marked with disrupted skin, lung and gut barriers, altered microbiome and local and systemic Th-2-driven immunological pathways. Those allergic conditions can comanifest or occur in temporal sequence. The hypothesis that has been proposed to clarify time sequence and associations of allergic disease is called allergic march. This concept means that allergic disorder starts in early infancy with the first hallmark of atopy and atopic dermatitis and then appears food allergy, and later in childhood comes asthma and allergic rhinitis. Some investigators presumed that the underlying allergic inflammation of the skin could progress from atopic dermatitis to asthma. In addition, some preventive measures like improving skin barrier before skin disease onset can reduce the risk for respiratory allergy. Those observations support the causal link between atopic dermatitis and asthma. Although described longitudinal appearance of all allergic diseases was noticed only in small proportion (~7%) of children [6, 7], others had different trajectories of one or more allergic diseases which can occur in different point of time in childhood. Last explanations are talking about a cluster of coexistence-related allergic diseases rather than a progression.

2. Atopic dermatitis, disrupted skin barrier and allergic sensitization: is it the beginning?

Atopic dermatitis is the most common chronic skin disorder in childhood. It appears in early childhood with dry, itchy skin and eczema on the cheeks, wrists and other parts of the body. Up to 20% of children experience AD in childhood. The majority outgrows eczema, but one proportion of them continues to have symptoms into adulthood [8]. According to the recently published cohort, six latent classes representing subphenotypes of AD were identified. These classes can be summarized in four classes as follows: unaffected individual or transient AD (61.9%); early-onset-persistent AD (10.7%); early-onset late resolving, early-onset early resolving and mid-onset resolving by age 11 years of age (16.5%); and later-onset AD after age 3.5 years (10.9%) [9].

AD is a systemic disorder characterized by disrupted skin barrier. It is considered that factors associated with damage of skin barrier are complex and influenced by a combination of structural, genetic, environmental and immunological factors. Structural changes are caused by altered lipid composition, decreased structural proteins, increased skin pH and reduced skin microbiome diversity. Cutaneous permeability defects can be assessed by measuring transepidermal water loss (TEWL) which correlates with disease severity. Several genetic defects encoding skin barrier proteins contribute to the breakdown of skin barrier. Inherited loss-of-function mutations in filaggrin gene, which encodes structural epidermis proteins, are

associated with early-onset AD that is more often persistent and closely related with asthma and food allergy [10]. Polymorphisms in the thymic stromal lymphopoietin (TSLP) gene, SPINK5 gene and corneodesmosin have also been linked to AD and the development of food allergy [11–13]. The inflammatory responses induced by AD are manifested by increased production of Th2 cytokines such as IL-4, IL-13, IL-25, IL-33 and TSLP. TSLP is one of the major inductors of systemic Th2 response, and it is considered that it could be the link between skin and respiratory allergy. It is expressed in skin keratinocytes, pulmonary airway and intestinal epithelium, while increased expression was observed in the skin of AD patients and respiratory epithelium of asthma patients [14].

Skin microbiome dysbiosis is characterized by the dominance of *Staphylococcus aureus* which through various mechanisms worsens chronic skin inflammation [15]. Skin barrier dysfunction is associated with innate immune activation that results in dysregulated immune response to environmental antigens (like allergens and bacteria) and skin inflammation leading to the evolution of allergic sensitization [16]. Several studies on animals and humans support the concept that damaged skin promotes sensitizations. In mouse, exposure to egg and peanuts through disrupted skin induces sensitization [17] and, after exposure to egg aerosol, could induce asthma-like airway hyperresponsiveness [18]. In children, applications of peanut oil to inflamed skin were positively associated with the development of peanut food allergies [19], and the use of wheat-containing facial soap was positively associated with the development of wheat food allergy [20]. Application of oat-based creams on the skin of children with AD can induce oat sensitization in one third of children [21]. The concept of allergic march has been supported by cross-sectional and longitudinal birth cohort studies. Several birth cohorts have shown associations between early-onset AD and development of asthma and allergic rhinitis in school age [22, 23]; risk is greater in children with early-onset persistent AD phenotype [24]. Children with AD and allergic sensitization had increased risk of food allergy, asthma and allergic rhinitis compared to non-sensitized children without AD [25]. Food sensitizations in the first 2 years of life were associated with increased risk of asthma and allergic rhinitis in school age [26]. Peanut, milk and egg food allergy also increased the risk of developing asthma and rhinitis later in childhood [27]. Meta-analyses of birth cohort studies which investigated atopic march observed that early-life food sensitization was associated with an increased risk of infantile eczema, childhood wheeze/asthma, eczema and allergic rhinitis and young adult asthma [28].

The development of sensitization is complex, and except skin barrier defect and environmental allergen exposure, the presence of other factors is important because they may function as adjuvants, and some of them are bacterial colonization of the skin, allergens with intrinsic protease activity and exogenous adjuvants [29].

3. Why is allergy increasing? Hypothesis-driven strategy

Allergic diseases of the skin, gut and lung are complex disorders with multiple phenotypes and underlying genotypes. They occur as a result of environmental exposures during early life in individuals with genetic susceptibility to allergy. Gene-environment interactions are accountable for different influences of the environment on individual level. There are several hypotheses of allergy increase in the twentieth century. According to the *hygiene hypothesis*, decreased exposure to microorganisms in modern society, through increased hygiene and decreased prevalence of infection in early life, disrupts immune tolerance and directs immunological reaction toward Th2 direction [30].

The beginning of hygiene hypothesis can be found in the David Strachan study from 1989. He observed that children who grew up in large families, with large number of older siblings, have less allergy and concluded that exposure to infection in early life (prenatally and early childhood) can prevent allergy [31]. This was confirmed by subsequent studies which linked less allergies with viral, bacterial or protozoic pathogens, transmitted by the fecal-oral route [32]. In 1990 hygiene hypothesis was supported by the observation that growing up on farms, regular contact with farm animals, stables and drinking unpasteurized milk were protective against allergy [33]. Farms are microbe-rich environment. Endotoxin, lipopolysaccharide, part of the outer layer of Gram-negative bacteria, is a marker of microbe surroundings. Its protective effect on atopy is produced by stimulation of immune system in Th1 direction. Preventive effect of endotoxin was seen only for early-life exposure (prenatal and early childhood, before development of allergic sensitization) [33, 34].

In the past 20 years, hygiene hypothesis was expanded by "old friends hypothesis" and "biodiversity hypothesis" [35, 36]. According to that hypothesis, contact with natural environment and its species (included microbes and parasites) protects against allergy. Children are exposed to the environment indirectly (through mother during prenatal life) and directly through the skin, gut and lung. Changes in the microbiome of the gut, skin and nose reduced microbiome diversity, and loss of symbiotic relationship with parasites and bacteria increased the risk for allergic disease [37]. Stability and diversity of gut microbiome are developed during early life (first 1000 days of postnatal life). This process can be influenced with different factors like mode of birth, infant feeding, fiber content in the mother's and child's diet and older siblings and exposure to pets and/or farm animals during childhood. Environment and dietary habits of mother and previous generations can change microbe diversity of neonate's trough epigenetic modification [38–42].

The second hypothesis *dual-allergen exposure hypothesis* is based on observations that allergic sensitization occurs through disrupted skin in AD, while early ingestion of food (before development of sensitization) allows development of oral tolerance [43]. Delayed introduction of solid food in infancy, which were recommended at the end of the twentieth was not protective for food allergy development [44]. This hypothesis was confirmed by several randomized clinical trials like Learning Early About Peanut Allergy (LEAP) and Enquiring About Tolerance (EAT). EAT was looking at the early introduction of six common food allergens at 3 months of age alongside breastfeeding compared to exclusive breastfed infants. It found that prevalence of egg allergy was lower among infants with early introduction [45]. LEAP assessed oral tolerance induction of peanut in group of high-risk infants between 4 and 11 months of age. It compared early and regular peanut consumption, average of 6 grams of peanut protein a week, in relation to completely avoiding peanut protein until 60 months of age. Early introduction of peanut protein results in significant reduction in peanut allergy. LEAP-On study was an extension of LEAP, in which protective effect of early introduction on peanut allergy was observed, even after cessation of peanut consumption [46, 47]. According to the findings from the studies like LEAP and EAT, guidelines for complementary feeding were remarkably changed. Pediatric and allergy societies have published consensus statements about early introduction of peanuts in high-risk infants. Also, current recommendations advise against delayed introduction of allergenic food into infant diet [48, 49].

Recent researches report about the important role of vitamin D in the pathogenesis of allergy. Vitamin D has positive impact on foetal lung development and an immunomodulatory effect; it stimulates differentiation of T lymphocytes, induction of Treg, while its deficiency induces Th2 response [50]. It was observed that rise in allergy prevalence occurs with increasing *vitamin D deficiency* especially among

populations less exposed to the sun [51]. Deficit of vitamin D is associated with increased risk of peanut and egg food allergy, atopic dermatitis and asthma. The severe form of the diseases was observed with higher vitamin D deficiency [52, 53].

4. Allergic march: causal link or cluster of related diseases

The allergic march is a real phenomenon, but there is a great debate about underlying mechanisms. Some researchers argue that there is a causal link between AD and other allergic diseases in childhood, in which AD is the first disease with local and systemic immunological response. Systemic response could trigger multisystem allergic disease. Longitudinal, prospective population-based cohorts or cohorts of high-risk infants reported about increased risk of asthma and allergic rhinitis among children with previous or current AD [54–59].

Meta-analysis of 13 prospective birth cohort studies reported that odd ratio of asthma among children with AD in the first 4 years of life was 2.14% (95% CI 1.67–2.75), while the prevalence of asthma at the age of 6 years in eczema cohort studies was 29.5% (95% CI, 28.2–32.7%). The conclusion was that only one in every three children with eczema develops asthma during later childhood [4]. According to the results of high-risk birth cohort, 26.7% children with AD developed AR at 7 years of age, while the risk is higher among children with persistent and late-onset AD (OR 2.68, 95% CI 0.97–7.41) [57]. Sensitization to food allergen increased the risk for AR (OR 1.2, 95% CI 0.6–2.2), but the associations is stronger among children who had co-sensitization to both food and aeroallergens (OR 3.1, 95% CI 1.2–7.8) [28]. In the PASTURE study, children with early-persistent AD phenotype and those with late phenotype had an increased risk of developing allergic rhinitis. Early AD phenotype did not associate with AR, while the risk increased among children with early AD and food allergy [60]. According to these results, there was a new question: can we predict which phenotype of AD will be linked to asthma? More information come from longitudinal cohorts which analyzed different phenotypes of AD based on disease course and determined which classes are at highest risk for other atopic diseases [9, 60, 61]. According to the results from those studies, the early-onset, severe, persistent phenotype is associated with the highest risk for allergic comorbidities. Polysensitization, atopic heredity and filaggrin loss-of-mutation contribute to increased risk [62]. Children with high-risk phenotype of AD are candidates for preventive measures, which could delay or stop the occurrence of asthma and allergic rhinitis. But, it is considered that there is not enough evidence that AD causes asthma and allergic rhinitis. Paller et al., in recent review, presumed existence of inherited predisposition to one or more atopic disorders. Occurrence of the disease is a result of complex interplay between different underlying genotypes and environmental exposures during maturation of immune system, with tissue-specific peak time of clinical manifestation. Allergic diseases have different phenotypes and different trajectories that form clusters [62].

Simultaneously with AR, local allergic rhinitis (LAR) can appear in the preschool age. This entity of rhinitis is marked with local synthesis of specific IgE but without systemic allergy (allergic sensitizations and specific IgE). It was observed that LAR is a separate, well-defined phenotype of noninfectious rhinitis, which is stable over time [63, 64]. But, among younger patients and children, LAR can be the first step in the natural evolution to classical AR, especially when starting in the first two decades of life and in polysensitized patients [65]. In the German Multicentric Allergy Study, it was observed that over one third of the children developing a typical grass pollen-related seasonal AR had no serum-specific IgE

to pollen. These children develop a systemic IgE sensitization to grass pollens in the second or third pollen season following the onset of their rhinitis symptoms [66, 67]. If patients with LAR have AR over time, this supports atopic march.

5. Can we prevent and/or stop atopic march?

Better understanding of underpinning mechanisms of atopic dermatitis and atopic comorbidities as well as environmental risk factors induces further researches of preventive interventions aimed at stopping atopic march. Those interventions could be started during pregnancy and early life among healthy or high-risk infants before onset of disease (primary prevention) or among children with one atopic disease in order to prevent appearance of other atopic comorbidities (secondary prevention).

Disrupted skin barriers promote sensitizations and increase the risk for allergic disease. Improvement in skin barrier through regular application of emollients beginning in the neonatal period can prevent AD among high-risk children. Protective effect was observed if treatment lasted up to 6–8 months of age [68–70]. There was favorable effect at the 12 months of age, even after treatment was ceased [69]. These researches support original hypothesis of skin barrier dysfunction as a beginning of atopy march, but it is still unclear if this protective effect is long-lasting or onset of AD is delayed. The effect of emollients on food allergy was unclear. Only one research showed a trend for decreased food sensitization at 6 and 12 months of age [69], while two other were not powered to measure food sensitization [68, 70]. Some of undergoing studies aim to investigate the effect of emollients in prevention of AD among general population.

Local and system inflammatory response is a hallmark of AD, and anti-inflammatory therapy is effective in control of exacerbations, but study of Schneider et al. showed ineffectiveness of pimecrolimus in stopping atopic march [71]. Skin microbiome dysbiosis can increase the risk for onset or exacerbation of AD and comorbidities [72]. Recent researches showed that topical application of skin commensal bacteria can improve lesions in AD [73, 74]. Apart from local use of bacteria, the great interest of researchers is the role of probiotics in protection of allergy. Several studies have shown positive effect of probiotics like that adding *Lactobacillus rhamnosus* in diet of pregnant women can reduce the risk of AD [75]. Adding probiotics like *Bifidobacterium lactis*, *Lactobacillus salivarius* or *Lactobacillus GG* to the infant formula reduced the severity of AD [76]. But recent randomized control trial has shown opposite result. The study concluded that early supplementation with LGG in the first 6 months of life does not appear to prevent eczema at 2 years of age [77]. However, systematic reviews and meta-analyses report protective effect of the probiotics for the primary prevention of atopic dermatitis [78–80]. Probiotics are ineffective in prevention of asthma, food allergy and allergic rhinitis. Medical societies like the American Academy of Pediatrics, the European Academy of Allergy and Clinical Immunology and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition do not recommend the use of probiotics for primary prevention of allergic disease [49, 81–83]. The World Allergy Organization recommends the use of probiotics in diet of mothers of high-risk infants during pregnancy and lactation and in diet of those infants in order to prevent AD [84]. There is no consensus for the most effective specific strain of probiotics. The strain, dosage, timing of introduction and duration of probiotics usage are still uncertain. These questions are the aim of the future investigations.

Early introduction of allergenic food like peanut and egg can prevent food allergy, but the effect on other allergic diseases is not known. Exposure to furry pets

in home like dogs and cats in early life can prevent sensitization, but this protective effect can be modified by endotoxin exposure [85]. Deficiency of vitamin D has been associated with onset and exacerbation of allergy. According to this immunomodulatory effect, it has been assumed that supplementation of vitamin D might protect against allergy. But recent researches does not support protective role of vitamin D in allergy [86, 87].

In the prevention of allergic diseases, protective effect was observed for antihistamines. In infants with atopic dermatitis or with high risk for allergy, ketotifen treatment was associated with lower incidence of asthma [88], while the use of cetirizine decreased the risk for asthma in grass pollen-sensitized children [89]. Allergen immunotherapy (AIT) has been used over the last 100 years and is the only therapy with disease-modifying effect. The role of AIT in primary and secondary prevention was investigated in several studies. Sublingual AIT applied for the primary prevention of allergy among high-risk infants has no protective effect on the developing of first allergic disease [90]. Oral AIT decreased the risk of asthma, among children with grass pollen allergic rhinitis [91]. Recent systematic review and meta-analysis found no evidence that AIT decreased the risk for developing a first allergic disease. However, AIT reduced the risk of asthma among patients with allergic rhinitis. This effect was observed 2 and more years after the AIT was completed. AIT can reduce the onset of new sensitizations, but the evidence was not clear [92, 93].

6. Conclusion

Allergic diseases like atopic dermatitis, asthma and allergic rhinitis have sequential appearance with typical peaks of incidence during childhood. This temporal association is observed in the whole children population, and it starts with atopic dermatitis and food allergy in infancy, followed with asthma in the preschool age and finishes with allergic rhinitis. During growing up, the remission of atopic dermatitis and asthma was noticed, while symptoms of allergic rhinitis persist through adolescence and young adult age. The occurrence of all allergy diseases among the same child in temporal appearance was noticed only in smaller proportion of children in which causal link between AD, asthma and AR can be presumed; while, among others, common occurrence of allergic diseases follows different trajectories, without typical allergic sequence. For those children, complex interplay of allergic predisposition, systemic and local immunological responses and environmental influences during maturation of immune system triggers the appearance of those coexistence of allergic disease.

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