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Probiotics in Prevention of the Atopic March: Myth or Reality?

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The objective of the paper is to investigate whether probiotic supplementation prenatally and/or postnatally could prevent the development of atopic/allergic march after systematically reviewed the literature. The atopic march refers to the natural history of allergic diseases which develop during infancy and childhood. Allergic diseases, including atopic dermatitis, IgE-mediated food allergy, asthma, and allergic rhinitis, have dramatically increased over the last century. It is now known that every fourth child is allergic, but assumed that in 2020 every second child will be allergic. Pub Med were searched for randomized controlled trials regarding the effect of probiotics on the prevention of allergy in children. Type 2 inflammation is the central tenet of the atopic march. Intestinal microflora play an important role in the Th1/Th2 balance. Probiotics are cultures of potentially beneficial bacteria that positively affect the host by enhancing the microbial balance and they restore the normal intestinal permeability and gut microecology. Therefore, the use of probiotics prenatally and postnatally may counterbalance the Th2 immune phenotype, thus preventing the development of the atopic march. Probiotics administration is able to reduce atopic inflammation and to enhance anti-inflammatory markers. **Conclusion** – The current systemic review suggests that probiotics administered prenatally and postnatally could reduce the risk of atopy and food allergy in young children, but they are not helpful in the prevention of asthma.

Introduction

The atopic march is a term that describes the progressive development of allergic diseases during infancy and childhood. Classically, the atopic march begins with atopic dermatitis (AD) and progresses to IgE-mediated food allergy (FA), asthma, and allergic rhinitis (AR) (1, 2). Allergic diseases have dramatically increased over the last century. It is now known that every fourth child is allergic, but assumed that in 2020 every second child will be allergic. Once an individual has commenced on the atopic march, it is difficult to stop the progression.

The objective of the paper is to investigate whether probiotic supplementation prenatally and/or postnatally could prevent the development of the atopic/allergic march, by means of a systematic review of the literature.

AD -the Gateway to the Atopic March

AD is considered to be the gateway to the atopic march. It is most commonly diagnosed in the first 6 months of life before the development other atopic diseases. AD results from a combination of primary disruption of the skin barrier (protein filaggrin) and under-

lying genetic and/or environmental predisposition for type 2 inflammation. The type 2 inflammation is the central tenet of the atopic march (1, 3). Polymorphisms in the gene that encodes thymic stromal lymphopoietin (TSLP) and its receptor influence AD risk, FA, and asthma (4) whereas polymorphisms in the genes that encode interleukin (IL) 33 and its receptor are associated with increased risk of AD and asthma (5).

AD and FA-Early Manifestations of the Atopic March

The presence and severity of AD positively correlate with the risk of developing FA. Children with AD are as much as 6 times more likely to develop an FA compared with their healthy peers (6). Food specific IgE responses can be detected in the first months of life and peak at approximately 10% prevalence at 1 year of age. The fact that sensitization occurs before food ingestion in most cases suggests that sensitization to foods occurs via exposure through inflamed skin, as opposed to the gastrointestinal tract (1). Positive correlations have been found between the use of wheat- or peanut-containing skin products and the development of wheat or peanut allergy (7). Exposure to peanut dust in a child's home positively correlates with the likelihood of developing peanut allergy (8). Allergen-specific T cells isolated from peanut allergic patients express skin-related homing molecules, providing additional evidence of the skin being the site of allergen sensitization in FA. These findings support the theory that there is transcutaneous sensitization to food allergens in susceptible individuals (1).

Asthma and AR-Late Manifestations of the Atopic March

AD is also strongly associated with the development of asthma and AR. IgE responses to inhalant allergens develop later in childhood, providing a possible explanation for the delayed age of onset of asthma and AR. Approximately 20% of children with mild AD develop asthma, more than 60% with severe AD develop asthma (1, 9). Respiratory allergy occurred in 50% of children who had onset of AD during the first 3 months of life and atopic family members, compared with 12% of children who had late onset of AD and no atopic family members (1). Children with AD have been shown to have more severe asthma than asthmatic children without AD (10). The German Multicenter Atopy Study (MAS) found that 50% of children with early AD and a family history of allergy had rhinitis or asthma, and 69% of infants who had developed AD by 3 months of age were sensitized against aeroallergens by 5 years of age (11).

Not every patient with AD develops asthma, and not every patient with asthma has preceding AD. A recent retrospective analysis of 2 birth cohorts found 8 separate patterns of atopic disease progression (12). This study found that 10.5% of respondents followed the atopic march, whereas 15.5% had persistent AD, 5.7% had wheeze without AD, and 9.6% had rhinitis without AD. These findings indicate that the atopic march is not present in all atopic individuals. The presence of FA is also an independent risk factor for the development of AR and asthma. In a retrospective birth cohort study of almost 30,000 children, Hill et al. (3) found that the presence of FA to peanut, milk, and egg was associated with development of asthma and rhinitis. They also showed that children with multiple food allergies were at increased risk of developing respiratory allergy compared with children with a single FA. The clinical association between asthma and AR is well established. AR is also positively correlated with asthma severity, and AR treatment improves asthma control (1, 13).

Immunological Mechanisms Underlying the Atopic March

Allergen exposure through inflamed skin is thought to be the primary route by which individuals initiate the atopic march. This hypothesis is supported by data from animal models that indicate that transcutaneous allergen exposure promotes the development of specific T- and B-cell responses and subsequent allergic disease. The inflammation observed in AD is associated with increased production of IL-4, IL-25, IL-33, and TSLP, which recruit IL-5 and IL-13 producing type 2 innate lymphoid cells, and contribute to the development of type 2 inflammation. Dendritic cells (DCs) and other immune cells (macrophages, mast cells, and innate and adaptive lymphocyte subsets) migrate from the skin to draining lymph nodes, where they stimulate naive T cells to differentiate into allergen-specific Th2 cells. Once allergen-specific Th2 responses are present, they can exert effects systemically. An additional mechanistic question related to the atopic march is whether the presence of one allergen-specific Th2 response potentiates to the development of additional Th2 responses. One mechanism by which this may occur is via a bystander effect, in which an existing inflammation acts as an adjuvant for the development of other Th2 responses. Basophils are one potential contributor to the bystander effect because they are potent sources of IL-4. Elevated IgE levels may potentiate basophil facilitated Th2 responses both in the skin and at distant tissue sites. Together, these observations offer one immunological mechanism by which the presence of a Th2 response to one allergen could potentiate the development of additional Th2 responses (1).

Prevention of the Atopic March

Can we prevent and stop the atopic march? There are two possible points of intervention that may reduce the incidence of asthma and AR: (I) primary prevention, where an intervention is introduced prior to the child developing eczema, which prevents both the onset of AD and the development of subsequent allergies; and (II) secondary prevention, where an intervention is applied after a child has developed AD but is yet to develop other allergic disorders. Primary prevention includes: building and maintaining the infant skin barrier function, the use of probiotics and prebiotics, breastfeeding and supplementation with vitamin D during pregnancy and early life, and early introduction of allergenic foods into the infant diet (14).

Probiotics and Allergic Diseases

Probiotics are cultures of potentially beneficial bacteria that positively affect the host by enhancing the microbial balance, and therefore restore the normal intestinal permeability and gut microecology. They also improve the intestine's immunological barrier function and reduce the generation of proinflammatory cytokines characteristic of allergic inflammation (15). Probitotics also shape the immune system by rebalancing the "Th2 bias" with which infants are born (16). In clinical trials probiotics appear to be useful for the treatment of various clinical conditions, such as FA, AD and AR, and in primary prevention of atopy (15).

In twenty-seven infants who manifested atopic eczema during exclusive breast-feeding, Isolauri et al. (17) showed a significant reduction in the SCORAD score and of eosinophil protein X in the urine in infants supplemented by extensively hydrolyzed whey formulas and Bifidobacterium lactis Bb-12 or Lactobacillus strain GG, compared to children supplemented by the same formula without probiotics. In infants with cow's milk allergy and atopic eczema (18), the addiction of Lactobacillus GG to an ex-

tensively hydrolyzed whey formula showed the significant improvement of atopic eczema and a decrease in the fecal concentration of α1-antitrypsin and tumor necrosis factor-α, suggesting anti-inflammatory properties. Interleukin-10 has anti-inflammatory properties by down regulation of proinflammatory cytokines and IgE synthesis. Pessi et al. (19) reported a significant increase in IL-10 concentration in the sera of nine children with AD and cow milk allergy, treated with Lactobacillus rhamnosus GG. Wang et al. (20) administered fermented milk with the addition of Lactobacillus paracasei-33 or placebo in eighty children suffering perennial AR. According to a modified pediatric questionnaire, the supplemented group improved its quality of life, compared to the placebo group. In children with AR, Bacillus clausii administration has always led to a significant increase in nasal total symptoms score, a decrease in nasal eosinophils and a reduction in the days of treatment with antihistamine (21). In another double-blind controlled trial, Kalliomaki et al. (22) gave Lactobacillus GG prenatally to mothers with a family history of atopic disease, and after birth to their infants for 6 months. The primary endpoint was atopic disease at the age of 2. The results show a significant increase in the frequency of atopic eczema in the placebo group versus the probiotic group, whereas the preventive effect of Lactobacillus GG was still effective after four years (23).

The immunomodulatory activities of Lactobacillus rhamnosus GG have been demonstrated in human milk too. In sixty-two mother–infant pairs, Lactobacillus rhamnosus GG administered during the 4 weeks before the infant's birth and during breast feeding (3 months) increased the immunoprotective potential of breast milk, as assessed by the enhancement of antiinflammatory TGFb2 in the milk of the mothers receiving probiotics v. placebo (24). The best results of maternal probiotic supplementation were found in children with an elevated cord blood IgE concentration.

Zhang et al. (25) showed through meta-analysis that probiotics administered prenatally and postnatally are effective in reducing the risk of atopy, particularly in families at high risk for allergy, and the risk of food hypersensitivity in young children. According to subgroup analyses, probiotics administered to both mother and child, or a longer duration of intervention may be more effective in preventing atopy. In addition, cesarean delivered children might particularly benefit from probiotic administration. Several mechanisms might explain this effect. First, by colonizing the mother prenatally by supplementing probiotics, favorable bacteria could be transferred to the infant during birth. In addition, immunomodulation of the mother and changes in her breast milk composition could benefit the infant with respect to allergy development. Second, the gut is the most massive source of postnatal microbial exposure and a critical source of early immune stimulation, and probiotic supplementation early in life may modulate the maturation of the immune response. Differences in the gut microbiota composition have been observed before the development of allergic symptoms in several studies (25). The underlying mechanisms whereby probiotics prevent atopy might include producing a shift of the Th1/l Th2 balance toward a Th1 response, and the consequent decreased secretion of Th2 cytokines, such as interleukin IL-4, IL-5, and IL-13, as well as decreased IgE, and increased production of C-reactive protein and IgA (26).

The PandA study (a mixture of probiotic bacteria: Bifidobacterium bifidum, Bifidobacterium lactis, and Lactococcus lactis was prenatally administered to mothers of high-risk children (i.e. positive family history of allergic disease) and to their offspring for the

first 12 months of life) showed a preventive effect on the incidence of eczema in high-risk children. This preventive effect seems to be established within the first 3 months of life together with significant changes in the intestinal microbiota and decreased IL-5 production (27).

Guidelines published in 2014 by the European Academy of Allergy and Clinical Immunology's Task force on the prevention of FA suggested that there was still no evidence to support the use of probiotics for FA prevention, primarily based on studies of probiotics and food hypersensitivity (28). Many studies demonstrated that the administration of probiotics is able to prevent the onset of allergic sensitizations and improve the symptoms of AD and AR; however, studies were published, too, that achieved negative outcomes (29, 30). West et al. showed the moderate benefit of probiotics for eczema prevention, whereas there was less evidence of any benefit for other allergic manifestations (30). Two recent meta-analyses concluded that there is not enough evidence to support perinatal probiotic supplementation in the prevention of childhood asthma or wheeze (31, 32). Maternal probiotic ingestion alone may be sufficient for long term reduction of the cumulative incidence of AD, but not other allergy related diseases (33). Wei et al. (34) performed a meta-analysis of randomized controlled trials to investigate whether probiotics are associated with a lower asthma incidence in infants. They showed that there was no significant association of probiotics with the risk of asthma or wheeze compared with a placebo. Subgroup analysis by asthma risk showed that probiotics significantly reduced wheeze incidence among infants with atopic disease, but no significant associations were found in the other subgroup analyses in terms of the participants receiving the intervention, the timing of the intervention, a prevention regimen, the probiotic organism, the duration of the intervention, and the duration of follow-up. These findings do not support the recommendation to use probiotics in the prevention of asthma in infants.

Conclusion

In conclusion, the current systemic review suggested that probiotics administered prenatally and postnatally could reduce the risk of atopy and FA in young children, and that they may be helpful in respiratory diseases, but not in the prevention of asthma. In general, the use of probiotics in the prevention of the atopic march is still a myth, but further prospective studies are needed to confirm or disprove this claim.

Conflict of Interest: The authors declare that they have no conflict of interest.

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