Development of Allergic Sensitization in Perinatal Period: Can It be Prevented?

Department of Pediatrics, Inje University Sanggye Paik Hospital, Seoul, Korea

Hyo-Bin Kim

Allergen sensitization is an important risk factor for the development of IgE-mediated allergic diseases. However, sensitization may also be present without clinical symptoms. From the population-based cohort BAMSE, 51% were sensitized at least once up to 16 years of age, but 23% of the children with sensitization did not develop any disease. Therefore understanding the natural course of sensitization and its association with allergic disease need to be studied, then this may permit the suggestions of preventive interventions.

IgE sensitization to food and inhalant allergens starts in the first few years of life, and it seems to be possible to predict whether a child will have symptoms later in life. Most of the children maintain their early acquired IgE sensitization, but also they continue to acquire sensitizations to additional allergens. Therefore before the first years in the life of children seem to represent a period of plasticity of the atopic immune system during which IgE sensitization occur. To prevent allergic disease, then we have to first search for the modifiable factors exposed during pregnancy or early-life of childhood that may be associated with allergic sensitization.

Majority of IgE sensitization in infancy is against food allergens, and the sensitization march most commonly begins with egg and milk. Their sensitization rate increases up to school age then it starts to decrease. Sensitization to peanut, soy and wheat appears to increase with age. During the first two years of life the sensitization rate to inhalant allergens is low and then increases steadily. Early sensitization to food allergens is a risk factor for sensitization to inhalant allergens at an older age, which may be a risk for the development of respiratory allergic diseases.

There are many studies searching for the etiology of allergic diseases, and the Canadian healthy Infant Longitudinal Development (CHILD) study is a multicenter prospective birth cohort study established to determine the root causes of allergic diseases in children. The authors reported in 2018 that the children with atopic dermatitis may progress to subsequent allergic diseases, such as asthma, allergic rhinitis, and food allergy, and allergic

sensitization in infancy enhances the associations.

Modifiable factors to prevent the development of allergic sensitization

1. Maternal diet during pregnancy

Maternal diet during pregnancy may be an important early life exposure that influences immune tolerance and the development of allergic diseases in the offspring. From the GUSTO (Growing Up in Singapore towards Healthy Outcomes) birth cohort study, the 'seafood and noodle pattern' was associated with a reduced risk of developing allergen sensitization at both 18 months and 36 months of age. No association was found between 'vegetable, fruit and white rice' and 'pasta, cheese and processed meat patterns' and allergic outcomes. Maternal diet during pregnancy can influence the subsequent development of allergic outcomes in offspring, therefore modulating the diet pattern could be one recommendation for prevention of allergic disease.

2. Vitamin D

The results from studies dealing a link between vitamin D status at birth and the development of allergic disease are inconsistent. The LINA cohort study (Lifestyle and environmental factors and their Influence on Newborns Allergy risk) reported that cord blood 25-hydroxyvitamin [25(OH)D] levels were positively associated with children's risk for food allergy and allergic sensitization within the first 2 years of life which can be an argument to vitamin D supplement and its protective effect against allergy. In contrast, Taiwanese birth cohort showed maternal vitamin D status was inversely related to allergic sensitization in the offspring. The most recent report from the VIDI (Vitamin D Intervention in Infants) study investigated the effect of vitamin D depending on the supplemental doses, and published high-dose vitamin D supplementation did not prevent allergic sensitization during the first year of life. In contrast, an increased risk of allergic sensitization in infants was associated with high cord blood vitamin D status, indicating a possible adverse effect of high vitamin D concentrations.

The molecular mechanisms of the immunomodulatory effects of vitamin D are not fully understood. Vitamin D has effects on the innate and adaptive immune response, and modulates T cell, dendritic cell, and B cell functions. In allergy area, vitamin D may be important in the maintenance of Th1-Th2 cells balance, and by modulating regulatory T cells. There are conflicting results on vitamin D and allergy, further studies on the vitamin D status between individuals owing to genetic and epigenetic factors may be needed.

3. Early introduction to complementary solid food

An age at introduction of complementary solid food may contribute to food allergy in infancy. In a recent

systematic review and meta-analysis, enrolled RCTs showed egg exposure from age of 4 months was associated with reduced egg sensitization (OR 0.76, 95% CI 0.51-0.95) and allergy (OR 0.63, 95% CI 0.44-0.90). Peanut exposure from age of 4 months compared to delayed exposure was associated with reduced peanut allergy (OR 0.28, 95% CI 0.14-0.57). Although there are some evidences for reduced risk of food sensitization for infants who introduced solids early, it is not clear for the optimal timing of the recommendations, therefore further studies are needed to be clarified.

4. Tobacco smoke and air pollution exposure

Exposure to tobacco smoke during the fetal period and thereafter has been associated with acute and long-term adverse health outcomes in children and adolescents. But the impact of tobacco smoke on IgE mediated sensitization is less clear from conflicting data on allergens. The etiological mechanisms may differ depending on timing of exposure is suggested. The BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) study reported that secondhand tobacco smoke in infancy increases the risk of sensitization to food allergens up to age 16 years.

Studies have shown that air pollutants can enhance allergic inflammation and induce allergic immune response. Whereas exposure to traffic-related air pollution (TRAP) has been shown that it negatively impacts on respiratory health, the role of TRAP in the development of allergic sensitization in children is unclear. However, a cohort of children aged 6-11 years with asthma, living in the Central Valley of California, showed higher exposure to CO during pregnancy was associated with an increased risk of sensitization to at least one outdoor allergen. In addition, in a multi-center Canadian birth cohort study reported that high NO2 exposure after birth, but not during pregnancy, increased the risk for development of atopy in 1-year-old children. Although sensitization is extremely low in infancy, the influence of TRAP during the prenatal period has to be suspected for the association between TRAP and immune modulation. Intrauterine and early childhood factors may influence the development of allergen sensitization.

5. Maternal allergen-specific IgG

From the ALADDIN cohort, allergen-specific IgG responses in the blood of mothers, cord blood, and breast milk were correlated and that profiles of maternal allergen-specific IgG reactivity could be detected in children up the age of 6 months, in agreement with what is known about maternal transmission of gammaglobulins and their half-lives. In the study, children whose mothers had high levels of IgG antibodies against an allergen in their blood did not have allergic IgE sensitizations against this particular allergen. Therefore, high maternal allergen-specific IgG levels during pregnancy can protect against allergic sensitization in the offspring, which might prevent allergic diseases. Flicker S. and coworkers studied the mother who received subcutaneous immunotherapy with birch and

grass pollen extracts before she became pregnant. IgE antibodies specific for the grass pollen was present in serum from mother but not in cord blood, whereas IgG1 and IgG4 reactivity profiles were detected in the mother's serum and in the cord blood sample, identically. Thus the results indicate that IgG antibodies are transferred from the mother to the child via the placenta, and prenatal induction of allergen-specific IgG antibodies protects against allergen-induced sensitization in the offspring. The studied child has not developed any allergy to the age of 2 years. Active or passive allergen-specific vaccination of mothers may represent a feasible strategy for the prevention of allergic sensitization in childhood.

Conclusions

As the prevalence of allergic disease rises worldwide, prevention strategies are importantly considered. Preventive strategies for allergies could be approached by primary or secondary prevention. Sensitization pattern seems to predict sensitization and symptoms later in life. Therefore the window of opportunity for primary prevention should be considered because optimal time may be different by allergens, such as food allergen and inhalant allergens. Guidelines should suggest better methods and critical period for action to prevent allergic sensitization which is a risk factor for the development of allergic diseases.

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