Effect of Early Life Events on Allergy

Prenatal and early postnatal factors

Georges J.A. Casimir
Professor of Clinical Paediatrics
Free University of Brussels (ULB)
Belgium

Introduction
During the last 25 years, a significant increase in the worldwide prevalence of allergic diseases was described, especially in children. To be efficient in allergy prevention, the pathogenesis and the natural history of the disease might be understand. However, despite the broadening of our knowledge on the immune system during the neonatal period, on the mechanisms of allergic sensitization, on the respective role of genetic and environment on the development of symptoms, we still don’t know what causes allergy and at what exact time in child’s life?

Nevertheless, patients and parents need to obtain the best informations in the field, ensuring that they can benefit from strategies that have the best chances to interfere with the natural history of the disease. That is the reason why we must based our recommendations on reliable and up-to-date literature indicating clearly their level of evidence.
Today, the concept of the Allergic March in children must be interpreted taking into account the current knowledge on genetic and environmental factors in the development of allergic disease. Clinical expressions from food allergy and atopic dermatitis to allergic rhinitis and asthma do not develop as a fixed sequence. The pathophysiological mechanisms and timing of sensitization are still largely unknown, while there is no consensus on the way to detect and/or to monitor this process. The allergic predisposition can lead to the expression of one or multiple clinical phenotypes at different times in the life, each one independent from the others and with different degrees of severity.

It seems that fetal life, birth and/or early postnatal period could be of crucial importance for the acquisition of a tolerance to major allergens. In this paper, we will analyze the data concerning early life events on allergy.

The prenatal period
Genetic of atopy is probably polygenic and depending of the polymorphism of several genes. For example, IRF-1 (interferon regulatory factor) gene variations influence IgE regulation and atopy. Set associations of polymorphisms are important in studying genetic associations for complex phenotypes, such as rhinitis and atopy. But until now the genes involved in the mechanism of atopic predisposition are still unknown. It is estimated that the number of genes contributing to allergy and asthma range between 50 and 100, the contribution of each of them is probably not higher than 5 percents. Atopy in the child was associated with male gender. On the contrary, many data suggest that maternal and not paternal factors, placental factors, or both have an impact on perinatal allergic sensitization.

Children who are sensitized to any allergens early in life have an increased risk of subsequently developing wheeze, airway hyper-responsiveness or rhinitis.
The timing of allergen sensitization is controversial, with conflicting data suggesting transplacental priming versus exclusively postnatal priming.

Resolution of this question is important in relation to rational design of allergy prevention strategies, for example allergen avoidance during pregnancy.

Recently, Rowe showed in a high risk birth cohort that house dust mite sensitization seemed to occur entirely postnatally. However, for food allergens, recent data show that the risk to develop allergy in the offspring is dependant from the ratio in n-6/ n-3 polyunsaturated fatty acids in maternal diet during pregnancy, leading respectively to increase or decrease of symptoms in the infant. It is not recommended to manipulate the diet of the mother during pregnancy on the basis of the available data.

Maternal atopy seems to modulate the developing immune response of the infant and increases the chances to present allergic manifestations in later life. Maternal IgE, IgG and amniotic fluid cytokines, combined with the presence of allergen in the feto-maternal environment are all possible factors involved in the ultimate outcome in terms of infant Th-1/Th-2 responses to common environmental antigens.

Animal models are studied notably to evaluate the modulatory potential of preconception immunization on the neonatal development of subsequent allergic responses to maternal allergen exposure; nevertheless in this human, particularly active disease at the level of mucous membranes, it is difficult to extrapolate observations made to the animal in rather relatively artificial conditions.

An interesting question related to the development of allergic disease is whether the fetus in utero commonly is exposed to sufficient quantities of allergens to induce specific IgE production and how much the mother’s immune responses can affect the developing fetal immune system?
After birth, it seems that many factors, as frequency and severity of infections and timing or intensity of allergen and animal exposures, continue to influence immune response.

**The birth and early postnatal period**

Patterns of neonatal exposure to microorganisms have changed substantially over the last 100 years, and it has been suggested that this has influenced the risk of immune-mediated disease. Viral infections could, depending on their nature and their circumstances of occurrence protect from atopy and inversely induce some sensitizations (respiratory syncytial virus). The mode of delivery could influence the future of the immune response in the child: Cesarean section is associated with increased levels of IL-13 and IFN-gamma, perhaps because of lack of labor and/or reduced exposure to specific microbes.

Cesarean section delivery may be associated with an increased prevalence of atopic asthma, but this finding remains controversial.

The gastrointestinal microbiota composition may be of particular interest, as it provides an early and major source of immune stimulation (microbes and endotoxin) and seems to be a prerequisite for the development of oral tolerance; that could be a determinant mechanism to control allergic diseases in normal population and perhaps to treat sick children.

Considering these observations, a lot of manipulations of flora in newborns, notably by giving formulas containing lactobacillus, were attempt to try to interfere with the natural history of the disease. But of course, these manipulations could be dangerous and must be done according to good clinical practices and ethical recommendations. Even if certain papers show an improvement of atopic dermatitis in infants treated by formulas containing lactobacillus, these studies do not support the hypothesis that sensitization to foods or atopic eczema in European infants in early life is associated with lack of any particular culturable intestinal commensal bacteria.
The role of endotoxin produced by gram negative microbes and the polymorphism of its CD 14 receptor was also pointed as one of the potential mechanisms of modulation for the immune response. Early endotoxin exposure may be a protective factor against atopy but a risk factor for wheeze in high-risk children, showing that the group of patients considered and its immune pattern before exposure may be considered to extrapolate the clinical response. The same discussion costs for the exposure to pets (especially cats and dogs) considered as dangerous for already sensitized patients, but which could be protective in “naïve immune” children. It cannot be recommended to introduce pets in the home as “preventive strategy”, and strict avoidance is clearly recommended when the patient is clearly allergic to cat or dog allergens.

Breastfeeding is proposed as the best mean to fed the infant during the 6 first months of his life.

It is difficult to analyse the effect of breastfeeding on the development of atopic diseases, especially because the epidemiological rigor of studies involving breastfeeding is compromised by the inability to ethically randomize subjects to breastfeeding or formula feeding. However, evidence-based data showed that breastfeeding appears to be associated with a lowered incidence of recurrent wheezing during the first two years of life, possibly by reducing the number of symptomatic respiratory infections in this period, as infections are a prominent cause of wheezing in infants.
The available literature supports the conclusion that exclusive breastfeeding for at least three to four months is associated with a reduced risk of developing atopic dermatitis in high-risk infants. But recent data showed that the relationship between breast-feeding and infant eczema in the first 2 years of life is also modified by maternal allergic status.

As Th1 pressure is considered as a protective control of atopic diseases, there is also a significant association between antibiotic use and day care in the first year of life and wheezing at 7 y but not at 3.5 y. This strengthens the argument that these factors increase the risk of asthma.

Besides, sleeping on a used mattress in the first year of life is a risk factor for wheezing at 3.5 and 7 y 8 and the degree of exposure to allergens themselves is usually proportional to the probability of sensitization.

Exposure to a high level of HDM allergens increases the burden of respiratory diseases in the early childhood and the effect is independent of maternal atopy, environmental tobacco smoking, and moulds in homes.

Thus, strict food and HDM allergen avoidance should be considered for prevention of allergy in high-risk infants.

Atopic dermatitis and food allergy are usually the first manifestations of the “allergic march” describing the natural history of allergy in early life.

Precocious sensitization against house dust mites and pollens in atopic dermatitis leads more frequently to asthma and justifies to realize skin prick tests very early in the life allowing to estimate this sensitization. Prevention and treatment of atopic dermatitis appears to be very important to reduce further allergic manifestations.

Early life dietary interventions which included breastfeeding, delayed solid food introducing, partially hydrolyzed formula feeding, and high risk food avoidance could reduce the risk of atopic eczema and food allergy development and was probably an effective primary intervention method for infants at high risk for atopy.
The concept of the avoidance of allergens is gradually replaced by the use of substances or molecules which can influence and modulate the immunity.

This shifting of allergy prevention research from avoidance to tolerance induction will hopefully allow us to reverse the epidemic trend of allergy diseases.

Atopy is also clearly associated to tobacco smoke exposure and higher maternal education, probably related to modern western style of life in industrialized countries. Tobacco smoke must be excluded during pregnancy and passive smoking totally avoided for infants and children. It increases inflammation, allergen specific sensitization and asthma.

Conclusions
Primary prevention for allergic disease involves interventions designed to block immunologic sensitization to allergens.
As eczema is strongly correlated to the development of precocious sensitization, it seems that early management of eczema might reduce the prevalence of sensitization in children.

The present report presents the accumulating evidence for gene-environment interactions in allergy and asthma pathogenesis.
The first 3 years of life are pivotal in determining allergic sensitization, symptoms and prognosis of wheeze, probably throughout life.
Further research requires focused hypotheses encompassing genes and the environment in which they are expressed.

References