

Editorial

T-cell reactivity in neonates: influence of environmental and genetic factors

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IgE-mediated allergy

The atopic constitution (1) is characterized by the capacity of an individual to evoke immunoglobulin E (IgE) production after exposure to common ubiquitous antigens, so called allergens. The IgE class of antibody binds with high affinity to Fc receptors on the surface of tissue mast cells and blood basophils. A later exposure to the same allergen cross-links the membrane-bound IgE on the “sensitized” cells, causing their degranulation and release of pharmacologically active mediators. These mediators include for example histamine and prostaglandins, which exert biological effects on the surrounding tissues. These allergic reactions cause symptoms ranging from hay fever, eczema and asthma, to life-threatening reactions such as systemic anaphylaxis.

In the last few years evidence has accumulated to suggest that allergen-reactive type-2 T helper (Th2) cells play an important role in the induction and maintenance of the allergic cascade. The Th2 like immune responses related to atopy (1) are also important for a successful pregnancy (2) and Th2-skewed cellular immune responses to common environmental antigens have been demonstrated to exist already *in utero* (3). Several reports have shown that the initial priming of the immune system to both inhalant and food allergens occurs during the prenatal period, and that proliferative responses to allergens can be detected already in cord blood mononuclear cells (CBMC) (4–6). In addition, the levels of the Th1-type of cytokine interferon- γ (IFN-

γ) have been shown to be lower in CBMC from children who later develop atopy, in both phytohemagglutinin (PHA) (7,8), and allergen-stimulated cells (8,9). This suggests that individuals who are especially prone to develop an IgE sensitization later in life have an altered balance between Th1 and Th2 types of cytokines already early in life (10). A better understanding of the regulation of these early Th1/Th2-type responses early would perhaps help in identifying factors which could be used as predictors for such a development.

Increased prevalence of allergy

The prevalence of IgE-mediated allergic diseases has dramatically increased during the last decade (11). Many possibilities have been suggested in search of the explanation for this increase. It is well established that a positive family history of atopic disease indicating the atopic constitution is an important risk factor for the development of IgE-mediated disease in the child, indicative of the involvement of genetic factors (12,13). However, despite significant progress in the genetics of allergic disease during the past decade, the biological relevance of the genes and genetic variations that have been found to be associated with expression of the allergic or asthmatic phenotype still remains to be determined (14–18).

With regard to inheritance one intriguing finding is the increased propensity of the child to develop IgE-mediated allergy if the mother, rather than the father,

expresses the atopic constitution. The maternal influence is most prominently seen in younger age groups (19–23), and would indicate that an atopic mother can modify the development of the infant's immune response towards the allergic phenotype. The maternal influence could be allergen-specific because of placental leakage of allergen, allergen-derived peptides, anti-idiotypic antibodies or allergen-antibody transfer (24). Alternatively, it could be nonspecific, through the cytokine environment at the maternal–fetal interface, or it could be due to factors that the child encounters during the postnatal period, e.g. through breast milk (25,26).

It is obvious that genetic factors are important determinants of allergic diseases. However, they can explain neither the increase in prevalence over the last decades nor the significant, and in part large, differences in prevalence between regions of similar ethnic backgrounds. This suggests a strong environmental influence on the expression of allergic diseases.

Environment and asthma

During the last decade a number of environmental and lifestyle factors have been found to be significantly associated with certain atopic phenotypes. Environmental factors shown to play a role include air pollution, traffic exposure, ozone and tobacco smoke. Besides passive smoking, which has been shown to increase the risk for asthma and bronchial hyperresponsiveness (27), no common factor has yet been identified. Rather, lifestyle factors such as early childhood infection, vaccinations, diet and family size seem to be of greater importance than pollution (27,28).

Gaining knowledge about the complex interplay between environmental and genetic factors would contribute to a better understanding of risk factors involved in the development of IgE-mediated diseases. This requires epidemiological and mechanistic studies on genetically similar groups.

Allergic diseases in East and West Germany

Epidemiological studies of IgE-mediated diseases have received much attention over the past decade (29). Some of the most interesting have been studies comparing the prevalence of allergies in East and West German populations after reunification (30–35). The beauty of these studies is that the two populations are very similar in ethnic and genetic background but have been exposed to very different environmental conditions for many years. Thus, the two populations are ideal to study dissociation of environmental and genetic factors.

Studies conducted shortly after the unification in 1990 reported lower prevalence of asthma, allergic rhinitis, and IgE sensitization both among children and

adults in East as compared to West Germany (30–35). The fact that there has been a subsequent increase in IgE-mediated diseases in East Germany since the reunion supports the facts that a “Western lifestyle” presents a greater risk for the development of allergic diseases (36–38). Similar increases have been reported in African communities where people moving from rural to urban areas also develop more allergic disease (39).

One interesting question arises: is the distribution of IgE-mediated diseases in East and West Germany different today, nearly 10 years after reunification? Published in this issue of *Allergy* is a prospective cohort study which aims to answer this question (47). Cord blood was collected from children living in Leipzig and Munich. The authors investigated levels of total IgE in cord blood as well as IFN- γ , tumor necrosis factor- α (TNF- α) and interleukin-4 (IL-4) expressing T cells after polyclonal stimulation. Based on questionnaires, they found that the frequency of double positive familial atopic heredity was significantly higher in Munich than in Leipzig. However, when correcting for this confounding factor the neonates from Munich had significantly less IFN- γ and TNF- α positive cells than neonates in Leipzig. This indicates that children born in Munich were more polarized towards Th2. A negative correlation was seen between numbers of IFN- γ and TNF- α cells and double atopic heredity which is in line with data reported by Gabrielsson et al. (40). Taken together the data suggest that the differences in the prevalence in IgE-mediated diseases between West and East Germany still exist.

The cord blood was collected between December 1997 and January 1999 and it would have been informative if data about correlation of cytokine responses and later allergy development could have been included, as previously shown by others (41,42). Cord blood IgE levels were initially believed to be a predictor for the development of IgE-mediated diseases (13). However, to date several groups have failed to find such an association (43), and there is a general agreement that cord blood IgE determination, used as a single test, is not suitable for allergy risk screening (44). The fact that there was no correlation between cord blood IgE and family history is in agreement with Gabrielsson et al. (40). Furthermore, the authors in this issue of *Allergy* (47) could not find a correlation between cytokine-expressing cells and cord blood IgE levels, which might indicate that cytokine production in cord blood and/or elevated levels of cord blood IgE might be a better predictor of the atopic constitution. However further studies are required before this can be established.

One interesting finding in the paper is that the frequency of parents with double heredity is higher in Munich. It would be interesting to evaluate whether this difference is dependent on genetic and/or environmen-

tal factors, by comparing the genetic set up in the two countries using candidate genes from the cytokine cluster on chromosome 5. This is known to be involved in regulating the balance between Th1 and Th2 cells and the production of serum IgE levels (45).

Concluding remarks

Taken together it is obvious that environmental factors play a significant role in the development of allergic diseases in genetically predisposed children. The influence of these factors seems to be greatest during infancy, probably a prenatal influence. A better understanding of the combined, complex network of genetic and environmental factors of importance for the

development of IgE-mediated diseases will require additional longitudinal epidemiological studies combined with mechanistic analyses. It is hoped that such studies will reveal information about factors for (atopy) development of IgE-mediated allergy at an early age and that this will lead to better prediction and intervention programmes.

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