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A GREAT DISCOVERY ALLERGY AND ASTHMA ARE FULLY GENETIC IN CHILDREN

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Abstract

Background. Allergic asthma and rhinitis, atopic dermatitis, urticaria and food allergy are genetic diseases of infants and children. Several investigators have provided evidence for a genetic localization for atopy. Babies of atopic parents are at high risk of developing atopic diseases, however the phenotypic expression of such diseases varies widely, being very mild in some infants and children, severe and frustrating in many, even life-threatening in others, being also common,disabilitating, and chronic.

Key words: genetic disease, atopic march, early onset, atopic dermatitis, food allergy, asthma, allergic rhinitis, infants, children

Introduction

Few diseases like atopic dermatitis, although not being lethal, are causes of invaluable physical and emotional suffering for either children or their parents. Needless to say, there are also growing numbers of wheezing infants at an early age. There appears to be a belief that asthma in children is increasing. Given the fact that the morbidity of asthma has not decreased despite many advances in pharmacologic treatment, it is clear that attempting at reduce exposure should come at an early stage of life (1). Actually, several data are explaining why atopic diseases are increasing in prevalence in Western countries: "Before birth" is the key, the suggestive site where the origin of atopy was recently unveiled (2-7).Therefore allergic and immunologic disorders, before being diagnosed in adult patients, start in the fetus, in the neonate, in the infant, that are the youngest pediatric populations. So very soon severe atopic disorders confront doctors with one of the most demanding challenges. Strongly associated is a positive family history (8), especially maternal in case of asthma (9), although several environmental

determinants have been reported (10).Several scientific advances have shed light in the past few years on the cell

interactions that is pivotal in orchestrating the inflammation underlying atopy. In particular we can now understand how strictly are linked with atopy the genetic factors: several cytokine genes are associated in the gene cluster of chromosome 5q23-q31, such as IL-3, IL-4, IL-5, IL-9, IL-12b, IL-13, and GM-CSF, together with the genes for the ß2-adrenergic receptor (11). There is a significant linkage between total IgE levels and several of these markers, particularly IL-4R (12) and IL-9 (13). A linkage of chromosome markers with bronchial hyperreactivity (BHR) and

total IgE concentrations has been reported (14). Two genes account for 78% of the genetic predisposition to high IgE levels (15). However this linkage has not been confirmed by others, either for total serum IgE or for BHR (16, 17) The genes for the ß subunit of the high affinity immunoglobulin E receptor (FceRI-ß) are located on 11q13 (18), and are associated, but without a complete unanimity of researchers, with one or more genes coding for atopy (11). The initial study showing a dominant gene on this chromosome (19) has been confirmed (20-24) or not (25-30),while an association between high serum IgE levels and D11S97 on chromo]some 11q

has been found in Japanese subjects (31). There is no association of atopic dermatitis with chromosome 11q (32), but with the FceRI-ß (33). Other genes located on 14q23, 14q32, and 14q11.2 may contain loci predisposing to high IgE levels, while those on 12q15 and 12q24 are associated with IFN-g concentrations (11) and show linkage with asthma and total serum IgE (34).Overall, a more suggestive link is an early sensitization within the first-third years of life mediated by indoor allergen exposure (35, 36).

Methods

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A meta-analysis was done of all available studies on the age of onset of the atopic march, without attempting at being comprehensive in this meta-analysis, but instead selecting what appeared the most relevant articles in the literature.

Results

In the first year of life, there is the onset of atopic dermatitis in 79, 8% (60, 2% to 100%), of cow's milk allergy in 72, 7%, egg allergy in 71%, and fish allergy in 51, 3% of babies. Asthma starts in the first year of life in 41, 8%, in the 2nd in 49, 3%, and within the 8th year in 92, 5% of children. Allergic rhinitis begins in 35% of babies in the 1st year of life, and in 59% or 13-19% in those aged 2-5 years. It seems therefore that the role of pediatric allergy and immunology has been hitherto somewhat obscured, as shown by the atopic march

Conclusion

It follows that this role is instead substantial, unmatched, focusing on the early and often very early onset of the atopic march, which needs strategic interventions in the very first months of life or even before birth. As the main goal of modern medicine is prevention of chronic and severe diseases, the possibility of preventing such disorders in predisposed children has stimulated the investigators' imagination since the beginning of the century, when atopic diseases were not as common as now.

Personal studies

In the following Table (37-58) we have meta-analyzed the results of several epidemiological studies, which enable me to present here a state-of-the-art report on the onset of the atopic march, focusing on the early and very early onset in several cases. When it is well known that atopic dermatitis (37-42) and food allergy (43-49) have

their onset within the first year of life in 70-100% of infants (37-42), and in the second in 69-96% of cases (43, 44), it may not be clear that allergy to a panel of foods begins before the first year of age in a wide proportion of babies (45-49).For example allergy to cow milk evidently begins in at least 72%, and to egg in 71% of infants (45-47). However the percentages of 52, 3% for fish, and of 62% for cereals can be unexpected, and even more the rates of legumes, fruits, and nuts (45-47). The case of peanuts depends on the country where the study was done (48, 49), whereas chocolate has been absolved (45).The asthma affair is a little more intricate: the onset within the first year is certain in 34, 5% (37, 38, 51, 52)-56, 2% (38, 54) of babies, but a higher level (82, 4%) is evident between the 4th and the 7th year (38, 54-56). That within the 8th Year the asthma onset is manifest in 90% of children (55) is confirmed by the 92% proportion reached in children less than 20 years of age (57). The sex difference may be 1,65:1 at 0-1 years, but it is inversely or practically abrogated within the 8th year (38).As regards allergic rhinitis, the onset may be in the first year in 35% of children and in 59% of those aged 2-5 years (38), who in other studies are affected in 13-19% of cases (37, 28). The sex difference is high between 4-10 years for males (2, 3:1), but in older children it seems to disappear (37).

Discussion

This meta-analysis was facilitated by the selection of only one factor, the age, though a cause of variability can be the wide range of disease definitions, especially for asthma. However only in preschool children, a definite diagnosis of asthma may be difficult to establish since many wheezing infants lose their symptoms in the first years of life (59). On the other side, lack of information on the development of the atopic march early in life may confound the interpretation

of early changes. Therefore, the role of pediatric allergists is also to be highlighted in view of the early onset of atopic disease, which stresses the pivotal and crucial place held by such specialists in the early diagnosis and treatment of young children.

The early onset of the atopic march (Table) is favored in the first place by cow milk allergy (45-47), a peculiar form of allergic disease in which IgE antibodies are directed to introduced daily proteins (4). The reduction of specific CD8 response could play a crucial role in the dysregulation of IL4 production in at risk babies, and probably in the breakthrough of oral tolerance towards cow milk proteins (4). Sensitization to foods occurs more commonly early in life, however occasionally it may even occur prenatally. Cow milk appears to be the most common offending food both in gastrointestinal (vomiting, diarrhea, etc.) and in cutaneous manifestations (urticaria and atopic dermatitis). Specific IgE to foods and positive challenge test to a number of food allergens are frequently present in children with such disorders. Food allergy and atopic dermatitis may negatively interfere with the child's life and his physical and physiological development. Prevention should be therefore the early mainstay of each intervention. According to previous and recent studies, prevention of atopic diseases in genetically predisposed newborn babies, is not only worthwhile (60) but also necessary. The family should have clear advice on the prevention of atopy (61). We have stressed the negative effects of the maternity wards. To avoid the possible risks it should be clearly stated that giving any formula in the first few days of life is strictly forbidden unless prescribed by a pediatrician or demanded by a mother who is unwilling or incapable to breastfeed her baby (62). It may also happen that 12/65 (18.5%) mothers included in a preventive program mistakenly eat cow milk and/or fish (63), or offsprings from bilateral atopic parents eat egg at the insistence of the

grandmother (62).A general improvement of the pediatric atopic population seems an unrealistic goal at the moment, however their management should be in the hands of well-trained pediatricians and pediatric allergists, and not in the hands of the various "alternative" practitioners using methods such as homeopathy, bioresonance,auriculo-acupressure, and the like (64), with serious and even dangerous results (65). We know that postponing the atopy development leads to a lessening of the severity of the clinical manifestations, and even to atopy avoidance forever (66).Once atopy develops; it is now possible to prevent the clinical manifestations in a great proportion of cases (secondary prevention) by the use of pharmacological agents such as cromons and ketotifen (66). In addition as demonstrated by the ETAC study, it is possible to prevent the onset of respiratory allergy in 50% of babies with atopic dermatitis following an 18-month administration of cetirizine (67). Since the commitment to the Th2 phenotype in atopic appears to occur at any time between the ages of 2 and 5 years (68), the net implication is that within the first years of life there is a window open for immunoprophylaxis (69). Moreover, dietary prevention is not sufficient if it is not accompanied by strict environmental measures. Possible obstacles confront any allergy prevention program (35, 36, 70), that should instead balance the contributing factors to the increase of indoor allergens (70). In the environment we find aeroallergens to be prevented, among which the leaders, such as house dust mite, pets, pollens, molds, cigarette smoke, and the indoor and outdoor air pollution (71-73). "An ounce of prevention is worth a pound of cure". If we cannot change the atopic inheritance after birth, we can start early and effective preventive measures also before birth. This issue appears to lay in a realm almost to be described as a "no-man's land". Mother Nature teaches that in the neonatal immature gut the first line of defense is formed by some specialized factors. It may be that this first line should be moved forward (74). I would like to stress, according to the Latin wisdom

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that stands on the portal of our Clinic "in puero homo ", which means "In infant is the seed of the future man", that the goal is not only to reduce morbidity and mortality, but mainly to insure the best quality of life both to infants and adults.

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