

REVIEW

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Risk factors for allergy

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Abstract Host factors involved in the risk for allergy are heredity, sex, race and age, with heredity being by far the most important. Exposure to allergens has been identified as an influential environmental factor, whereas passive smoking and pollution may act as an adjuvant. The atopic mother may – during pregnancy – add to an atopy-prone environment. Whereas respiratory infections are associated with attacks of bronchial asthma, infections in early life might play a role in the protection against atopy by preferential stimulation of a Th1 response, with mutual down-regulation of the Th2 response.

Conclusion Recognition of the risk factors for allergy is important in order to select the factors that could be modified for individuals at risk and in order to identify those factors of which the modulation could evolve in general preventive measures.

Key words Allergy · Risk factors · Heredity · Allergen exposure · Infections

Abbreviations *IFN-γ* interferon-gamma · *RSV* respiratory syncytial virus

Introduction

Allergic diseases are highly prevalent and apparently their prevalence is increasing in developed countries [10]. Recognition of the risk factors for allergy is important in order to identify factors that could be modified and in order to select individuals who could benefit from preventive measures.

Risk factors for allergy can be considered under two general categories, namely host and environmental factors. Some environmental determinants for allergy are modifiable and have been the target of preventive measures. Host factors are presently not modifiable. Risk factors can be primary, i.e. affect the incidence of atopic disease, or secondary i.e. enhance allergic sensitization or trigger symptoms in an already sensitized person.

Host factors**Genetics**

The most important single factor statistically associated with the development of allergic disease is the presence of other affected family members: a child with no atopic parent has a risk of 9% to 18% to be atopic, whereas the risk increases to 50% when one parent is atopic and to 70% when both parents are atopic [12, 79]. This family risk for atopy is determined by genetic and environmental factors. The plainest evidence for the genetic basis of atopy is provided by twin studies [27, 33]. From studies on monozygotic and dizygotic twins, reared apart and together, it became apparent that the total IgE level is largely genetically determined, but that sensitization to specific allergens is highly,

although not entirely, dependent on environmental factors. The degree of heritability of serum IgE levels lies in the range of 50% to 80% [33]. Different regions on chromosomes have been identified as being involved in the genetics of atopy: 5q31–33 and 11q13 are of major interest for the determination of the total IgE level [14, 15, 20, 42, 60]. The 5q31–5q33 region contains a cluster of genes encoding for Th2 cytokines IL-13, IL-4, IL-5, IL-3 and IL-9 as well as many other candidates [42, 56]. Chromosome 11q13 has been linked to the locus encoding the β -chain of the high-affinity IgE receptor [15, 60]. Linkage of atopy to maternal alleles on chromosome 11 could, with other factors discussed below, account for a higher atopy risk in children of affected mothers compared with children of allergic fathers [15, 60]. Whereas total IgE is largely determined by genetic, non HLA-linked factors, the genetic control for specific IgE may not be as important, but it clearly has some role, especially in patients who are mono-sensitized, and it appears to be associated with HLA class II genes located at chromosome 6p21–3 [77, 81]. Chromosome 14q12 has been shown to be linked to total serum IgE as well as to specific IgE [46]. Conflicting results probably reflect the presence of many susceptibility genes for atopy, each having a relative modest effect [56]. In view of the complex biochemical and immunological aberrations associated with atopy, a complex inheritance is not surprising. The family risk for atopy is associated with a delayed postnatal maturation of T-cell competence. Interferon-gamma (IFN- γ) production by T-cells is significantly lower in infants with a family history of atopy, compared to controls [31]. Several authors also found a significantly lower IFN- γ production by cord blood mononuclear cells in neonates with a family history of atopy [55, 70]. An impaired function or a delayed maturation of memory T-cells and not of naive T-cells seems to be responsible for the impaired IFN- γ production in those infants [52]. On the other hand, cord blood and peripheral mononuclear cells of atopy prone neonates and infants showed a higher proliferation response to antigenic stimuli, with specific responses to offending allergens [38, 45, 70].

Sex

Boys run a higher risk for atopy than girls. A higher sensitization rate in boys as compared to girls for house dust mite, grass pollen and cat epithelium can account for this sex difference [39, 57]. This can also partly explain the increased risk of asthma in boys [57]. Although this sex difference decreases in adulthood, most authors report a higher total IgE and a higher prevalence of specific IgE antibodies and of skin test positivity in men than in women [4, 23, 48]. Nevertheless, disease incidence for some atopic diseases – at least for asthma – seems to reverse in young adults [2].

Race

Racial differences in the occurrence of asthma and hay fever are difficult to interpret, as it is difficult to separate environmental influences and changes induced by migration from racial factors. Total IgE levels have been reported to be higher in black people than in Caucasians [25]. In the UK black children born in the UK seem to have asthma more frequently than white children and much more than black children born outside the UK. Black students in American universities have about the same frequency of asthma and hay fever as others, whereas Chinese students in midwestern universities suffer more frequently from ragweed hay fever [36].

Age

The risk for allergic sensitization and atopic disease varies with age. Susceptibility for allergic sensitization is particularly high in early life, especially in children with a family history of atopy [16, 28, 63]. Cross-sectional and longitudinal studies have shown that IgE levels are highest in childhood and fall rapidly between the ages of 10 and 30 years, whereafter the decline gradually slows [4, 28]. The highest incidence of skin-test positivity is in childhood, although conversion of skin tests from negative to positive continues at all ages up to the age of 55 [4]. Eczema is a disease of early childhood starting before the age of 5 in 87% of patients with adult eczema, and with frequent remission before adulthood [53]. Gastrointestinal allergic disease has its highest prevalence in infants and toddlers [8, 34]. The incidence of asthma is highest before the age of 10 and the peak prevalence of hay fever is highest in children and young adults [36].

Environmental factors

The atopic mother

The atopic mother is not only a genetic but also an environmental determinant. During gestation, there is an imbalance in favour of Th2 cells, which could be strengthened by Th2 cytokines of the atopic mother [71]. Such an environmental influence may explain, besides genetic factors, the higher incidence of atopy in children born to atopic mothers as compared to children of atopic fathers [40].

Until now it is not clear if differences in the serum phospholipid levels of babies born to allergic mothers are due to a different environment as to inherited factors [78]. The same applies for an association between large head circumference at birth and an increased risk for asthma in childhood [22].

Exposure to allergens

Exposure to allergens, especially in early life, is an important risk factor for allergy. A significant correlation has been found between sensitization for birch and mugwort pollen, as measured by skin prick test, and the season of birth [6, 7]. A similar correlation has been shown between birth at the end of the summer and housedust mite sensitization [24]. In atopic children early exposure to cats and dogs has been shown to correlate significantly with sensitization to cat fur and dog epithelium [18, 69]. The risk for housedust mite sensitization in childhood increases with exposure to higher levels of housedust mite in early life and correlates with a higher risk for the development of asthma [63]. Also severity of asthma increases and onset of asthma takes place earlier with exposure to higher levels of housedust mite in early life.

In infants at risk for atopy, a combined regimen of maternal and infant food allergen avoidance, including an extremely hydrolysed milk during the 1st year of life, resulted in a significant reduction of food allergy and of atopic dermatitis up till the age of 2, as compared to infants at risk fed a normal regimen [80]. However, at the age of 7 years, no significant difference in the prevalence of atopic diseases existed between the groups. In another prospective study, following atopy-prone children up to the age of 5, a significant reduction in the prevalence of asthma and of eczema was noted in the children who received breast feeding or a partial hydrolysate until 6 months of age, compared to children fed a conventional cow's milk formula or soy formula [12]. As the criteria for the family risk of atopy were less stringent than in the former study, it is difficult to compare the results of both studies. Introduction of solid foods into the diet before the age of 4 months seems to raise significantly the risk for eczema in the first 10 years, with a linear relationship to the number of foods introduced [21].

Passive smoking

Passive smoking undoubtedly is an important risk factor for asthma [26], but its association with allergic sensitization is less clear. There might be a synergistic effect of passive smoking with other risk factors as damped house or poor ventilation [3]. Differences in sex and race may also account for different results. Concerning the effect of maternal smoking on cord blood IgE, two authors, who controlled smoking habits of pregnant mothers by nicotine levels, were not able to detect significant differences in the cord blood IgE level of children from smoking and non smoking mothers [49, 50], whereas other studies, although not controlled this way, do mention a higher sensitization risk for babies born to smoking mothers [26].

In adults, smoking is associated with higher levels of total IgE [72], but its relationship with confounding vari-

ables as age, sex and others is complex and its effect on total IgE levels within populations is probably small [4, 23, 48, 59]. As to the effect of smoking on specific sensitization, an inverse relation has been shown with grass and birch sensitization, but as this was done in a cross-sectional study, a healthy smoker bias may exist [48].

Pollution

Air pollution may act as an adjuvant factor for allergic sensitization. Particulate pollution and photochemical smog are the most important outdoor air pollutants. They both have been linked to the incidence of asthma and other respiratory diseases [68].

Epidemiological studies in Japan have shown that people living within 200 m of main roads with heavy diesel traffic, are much more likely to develop allergy to cedar pollen than people living near cedar woods [35]. Other investigators found a similar correlation [9, 73] although Strachan could not detect consistent urban-rural gradients in the prevalence of hay fever and asthma [64]. The adjuvant effect of diesel particles may be the result of a direct effect of the aromatic hydrocarbons on B-cells, leading to enhanced IgE production, as was shown in vitro in humans [66]. Another mechanism could be physical interaction between pollutants and pollen grains, by binding pollen to diesel exhaust carbon particles of respirable sizes, making the pollen more allergenic [37].

Combined exposure to nitrogen and sulphur dioxide enhances the bronchial response to housedust mite allergen [19].

Infections

Respiratory infections, especially viral infections, are associated with attacks of bronchial asthma [11] and they also have been associated with the onset of allergic sensitization. In children the association of wheeze and respiratory infection can be explained by the unmasking of asthma in susceptible individuals, rather than by direct causation [44]. Temporary elevation of serum IgE during acute viral infections is well recognized in children and adults [51]. IgE antibodies to pertussis toxin have been reported during pertussis infection [29] and respiratory syncytial virus (RSV) IgE responses have been observed during RSV infection [75]. From a prospective study it has been concluded that RSV bronchiolitis during the 1st year of life is an important risk factor for the development of asthma during the subsequent 2 years and that it is associated with an increased frequency of allergic sensitization, especially in children with a family history of asthma or atopy [62]. More recently it has been shown that RSV bronchiolitis also induces a pronounced production of IgA antibodies, which gives further support to the hypothesis that RSV has a particular ability to activate Th2 cells [65], which

may be due to the occurrence of a particular glycoprotein on the surface of the virus [1]. Although these findings lend further support to a causal relationship between early RSV infection and development of allergy in later life, a firm relationship has not been established [74]. There is no epidemiological evidence suggesting allergic sensitization by respiratory infections in general [13]. On the contrary, infections may prevent allergic sensitization as suggested by earlier population studies as well as by recent studies on the prevalence of a positive skin prick test [43, 64, 67]. Martinez [43] reviewed the population studies of Anderson in New Guinea, of Mantle and Pepys on the Island of Tristan de Cunha and of Brown in the Western Carolina Islands, where a very high prevalence of asthma was associated with a very low prevalence of respiratory infections, in contrast to the situation in nearby less isolated populations belonging to the same ethnic group and with the same standard of living. In the latter a much higher prevalence of respiratory infections was accompanied by a much lower prevalence of asthma. Two recent studies in Western countries found an inverse relationship between the prevalence of allergic sensitization and allergic disease and the number of siblings [64, 67]. It was suggested that a higher incidence of respiratory infections brought about by the older siblings, protects against the development of allergy by stimulating a Th1 cell response with mutual down-regulation of the Th2 cell response. The finding that children who have had natural measles infection have a lower prevalence of sensitization to common allergens [58] and that in Japanese children delayed hypersensitivity to tuberculin is inversely related to the presence of asthma and serum IgE concentration [61] are concordant with these hypothesis. Maybe the inverse relation between infection and allergic sensitization is one of the explanations for the increase of asthma and atopy in Western countries, as in these countries the prevention of infection is one of the goals of modern medicine. It has been suggested that — besides respiratory microbial agents and probably more importantly — the commensal microbial flora of the gastro-intestinal tract may provide an important stimulus for the functional maturation of the immune system [5, 32]. Microbial products of the gastro-intestinal flora may activate the antigen presenting mechanism of dendritic cells, polarising towards a Th1 memory [30, 54]. In early life Th1 and Th2 cell populations do retain the potential of reversibility towards the alternate cytokine type and this reversibility is lost after long term stimulation [47]. This polarization toward a Th2 phenotype in atopics seems to occur between the ages of 2 and 5 years [76]. Possibly a preferential enhancement of the Th1 response through microbial stimulation, may have contributed to the significant decrease in atopic eczema in babies fed an extremely hydrolysed milk enriched with *Lactobacillus*, compared to atopic controls fed an extremely hydrolysed milk only [41]. An immuno-modulatory role frequently has been reported for *Lactobacillus*, but its cellular basis is up till now not fully

understood [5]. Recently it has been shown that lactobacilli are able to increase the IFN- γ -dependent activation of intestinal epithelial cells [17].

Conclusion

Heredity is by far the most important host factor for the development of allergy and exposure to allergens is a significant environmental determinant of the risk for allergy, whereas pollution and smoking seem to act as adjuvant factors. On the other hand, microbial stimulation in early life, by infectious agents and by the commensal microbial flora of the gastro-intestinal tract, may play a role in the protection against atopy by preferential stimulation of a Th1 response, with mutual exclusion of a Th2 response. It may be hypothesized that the decreased impact of infection through social changes and preventive measures may contribute to the rise of atopic disease in industrial countries.

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