

The allergy march: from food to pollen

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Abstract

There is epidemiological evidence, especially from longitudinal studies, that clinical manifestations of atopy as well as IgE antibodies against food and aeroallergens show a systematic sequence of events. The atopic march begins with food allergy associated gastrointestinal disorders and atopic dermatitis followed by respiratory allergies, i.e. asthma and atopic rhino-conjunctivitis. Detectable food antibodies, especially against egg and milk proteins, usually precede or accompany the early clinical symptoms and signs. Similarly, aeroallergen sensitization, first against indoor allergen antibodies, succeeded by outdoor allergen antibodies, precede the clinical manifestation of respiratory allergy. Early atopic events, either manifestation or sensitization can be used as risk markers or even predictors of atopic disorders to implement preventive measures. Early atopic dermatitis as well as elevated serum IgE antibodies against food allergens in the first two years of life in combination with a family history can be used as a predictor for aeroallergen sensitization. © 1997 Elsevier Science B.V.

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1. Introduction

The immunological mechanisms in the early development of atopic diseases are still not fully understood. However, epidemiological evidence, especially from longitudinal studies, suggests that there is a systematic sequence of events, which probably reflects the immunological maturational processes as well as the sequence of exposure against specific allergens. The intrinsic law is ruled by different genes, which control the immunological events leading to various clinical phenotypes and laboratory markers of the disease process. These epiphenomena of the real events can be measured in epidemiological studies.

2. The natural course of atopic manifestations

The natural course of clinical atopy in infancy and early childhood can be traced from longitudinal studies.

The early studies investigated the influence of early nutrition, beginning with the pioneering work of Gruleé and Sanford (1936) and followed by numerous other studies (reviewed in Burr, 1983; Kramer, 1988; Zeiger, 1995a). After the discovery of IgE in the late 1960's, the development of atopic diseases in relation to IgE values during infancy (Kjellman and Johansson, 1976) or to family history and IgE at birth (Kjellman and Dalen, 1986) were the objectives of cohort studies (reviewed in Bousquet and Kjellman, 1986; Bousquet and Michel, 1995). According to these studies, the natural course of atopic manifestations usually begins with food allergy-associated gastrointestinal disorders and atopic dermatitis and is followed by respiratory allergies, i.e. asthma and atopic rhino-conjunctivitis (nicely depicted in the study by Saarinen and Kajosaari, 1995).

3. The natural history of IgE sensitization

While transient low levels of serum IgE antibodies (<0.35 PRU/ml) were encountered even in children without current or later clinical atopy, high or long

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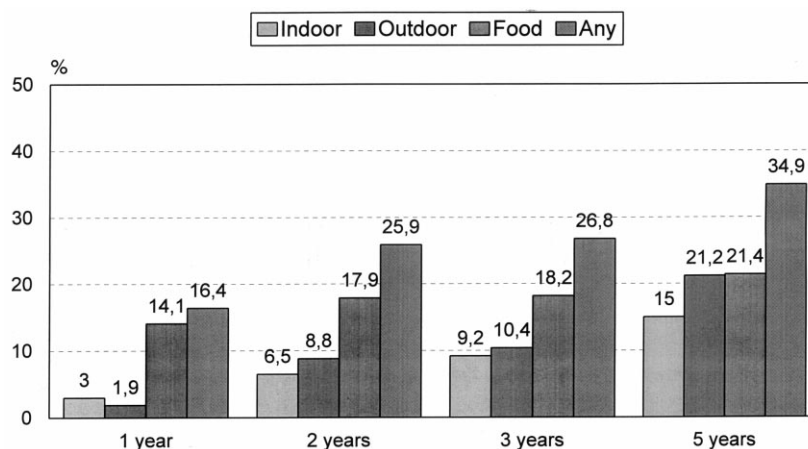


Fig. 1. IgE-antibodies (CAP Pharmacia ≥ 0.35 kU/l) against any of four food allergens (milk, egg, soy, wheat), any of three indoor allergens (cat, dog, house dust mite), either of two outdoor allergens (birch, grass) or any of all nine allergens in the first 5 years of life. Data from the MAS-90 study (Wahn et al., 1997a).

lasting elevated serum IgE levels were seen in atopic infants and children (Hattevig et al., 1987). In infancy, food antibodies, especially egg and milk specific IgE antibodies, were detected by skin prick tests or radioallergosorbent tests on subjects with immediate food hypersensitivity or atopic dermatitis (Van Asperen et al., 1983; Bock and Atkins, 1990; Guillet and Guillet, 1992), infants with an atopic family history (Van Asperen and Kemp, 1989; Piccini et al., 1993), or a mixed risk group (Hattevig et al., 1987, 1993). The highest prevalence rates for egg and milk antibodies were observed between 8 and 12 months of age (Rowntree et al., 1985; Hattevig et al., 1993).

Antibodies against aeroallergens were rarely detected in infancy, and the prevalence rates were low (Dela-court et al., 1994). The prevalence of aeroallergen sensitization increased from 2 years on in children with atopic parents or mixed atopy risk (Rowntree et al., 1985; Hattevig et al., 1993; Sigurs et al., 1994; Wahn et al., 1997a,b) (Fig. 1), children with atopic dermatitis (Guillet and Guillet, 1992), and children with asthma (Niemeijer and Monchy, 1992). While the prevalence of antibodies against food allergens in atopic children decreased, antibodies to inhalants did not disappear during childhood (Kjellman and Johansson, 1976; Guillet and Guillet, 1992; Hattevig et al., 1993). After childhood, the prevalence rates decreased in asthmatic patients (Niemeijer and Monchy, 1992). IgE antibodies to foods and inhalants more often preceded the clinical manifestation of atopy than vice versa (Foucard and Sjöberg, 1987; Hattevig et al., 1987; Sigurs et al., 1994).

4. Prediction and prevention of atopic disorders: from food to pollen allergy

4.1. Primary prevention

The systematic sequence of atopic disorders stimulated the concept that primary preventive measures should be tailored to the next expected atopic event. Elimination diets for the prevention of food sensitization or food allergy were therefore started soon after birth. Some studies evaluated the effect of elimination diets during pregnancy (reviewed in Zeiger, 1995a). The prevalence of food related atopic disorders could be reduced by elimination diets in infancy, but not by diets in pregnancy. The effect waned after discontinuation of the avoidance program (Fälth-Magnusson, 1994; Zeiger, 1995b).

Dietary avoidance had no effect on respiratory disorders (Zeiger, 1995a). In the Isle of White study, primary indoor allergen prevention, along with a food avoidance regimen, reduced the prevalence of aeroallergen sensitization and asthma (Hide et al., 1994; Hide, 1995). Notably, the avoidance regimen had been carried out in infancy, at an age when inhalant sensitization was not yet expected. This is in line with the observations that early exposure to inhalants in infancy had late and long lasting effects upon the occurrence of atopic airway disorders (Settipane and Hagy, 1979; Björkstén and Suoniemi, 1983; Croner and Kjellman, 1986; Quoix et al., 1988; Sporik et al., 1990; Arshad, 1991; Wahn et al., 1997a). Recent findings suggest that 'priming' of neonatal T-cells against inhalant allergens might already occur in utero (Holt et al., 1990; Piccini et al., 1993;

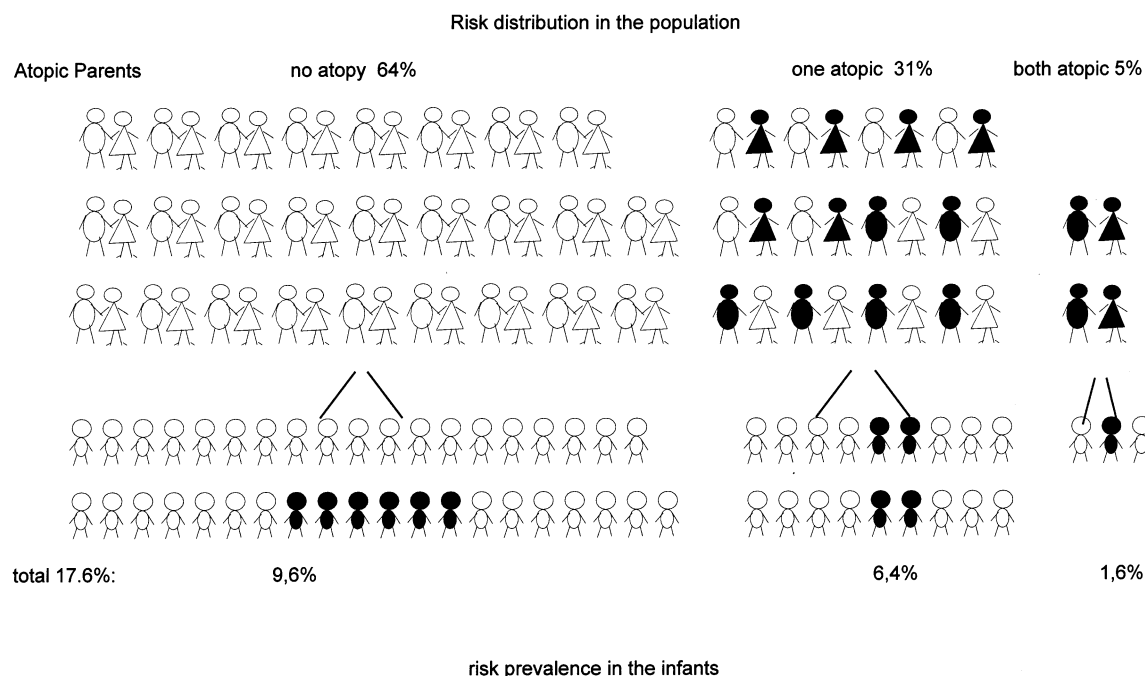


Fig. 2. Distribution of atopy risk in parents of 7609 German newborns according to questionnaire data and calculated distribution of atopic diseases in their infants during the first 2 years of life. Calculation of atopic diseases in infants has been performed by extrapolating the disease frequency in the MAS-cohort to the disease frequency in the recruitment area using the appropriate parental risk distributions. Atopic disease of the infant was defined as clinical manifestation of atopic dermatitis, recurrent wheezing, food intolerance, atopic rhinitis, and conjunctivitis in combination with detectable serum IgE antibodies (CAP-value > 0.35 kU/l) against at least one of nine allergens (Bergmann et al., 1997).

Warner et al., 1994). Therefore, primary preventive measures against aeroallergens should also be started in infancy.

4.2. Selection of subjects for primary prevention

Before recommending preventive measures, the subjects at risk have to be identified. The following questions will have to be answered: Which predictors are available at specified ages? How precisely can they predict the atopic disease to come next? What kind of preventive procedures can be recommended with regard to the age of the subject and the precision of the prediction?

The multicentre allergy study MAS-90 is an observational birth cohort study in Germany, rich with infants at high atopy risk (Bergmann et al., 1994). The study demonstrated that, on a population basis, most infants with atopic manifestations and sensitization in the first two years most likely do not have atopic parents, although the association between parental history of atopy and atopy in the infant is highly significant (Bergmann et al., 1997) (Fig. 2). Even when the close association between phenotypes in infants and their parents is taken into account, the predictive capacity of the parental atopic phenotype or of cord blood IgE in the cohort might be too low to justify invasive primary preventive measures in still symptom free infants (e.g.

removing pets and carpets, using feeding formulas not designed for healthy infants or excluding valuable foods from the diet of mother and infant). At this level, an allergy-preventive life style should probably be pursued by all families as well as recommended to all infants in the community (e.g. exclusive breast feeding for 4–6 months, tobacco smoke-free environments, healthy living conditions) (Rose, 1981).

4.3. Selection of subjects for secondary prevention

As soon as transient atopic symptoms and signs develop, secondary preventive measures can be introduced (Zeiger, 1995b). Even demanding measures will be better accepted and appear more justified in infants who have already suffered from early atopy with a high predictive capacity of clinical and laboratory markers.

In the MAS-90 study, 25% of children with a negative family history and who were egg sensitized at one year of age were found to be sensitized against indoor allergens at 3 years (OR 4.5, 95% CI 1.8–11.2) and 15% had outdoor allergen sensitization at 3 years. The risk of aeroallergen sensitization (either indoor or outdoor) at 3 years in infants who had a positive family history of atopy and a CAP-value above 0.2 kU/l for egg antibodies amounted to 70% (Nickel et al., 1997). This means, that infants with positive family histories of atopy and a high serum IgE-value for egg antibod-

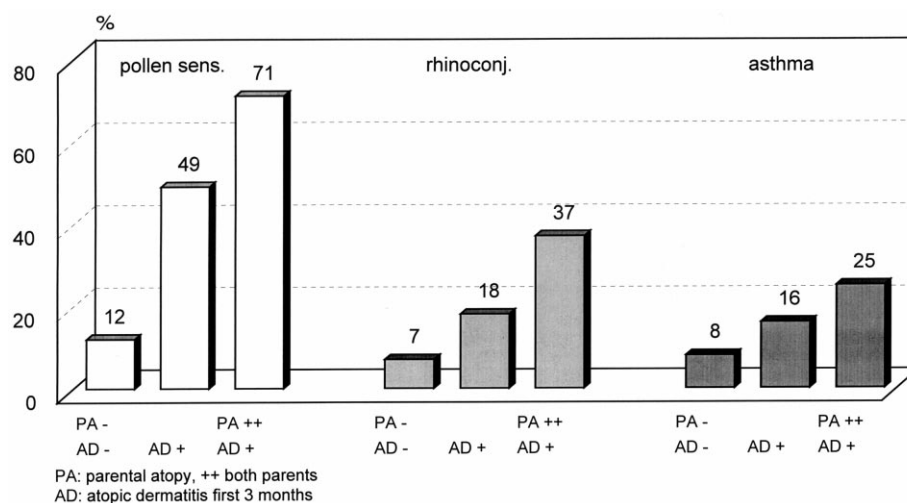


Fig. 3. Prevalence of sensitization to pollen (pollen sens.), of atopic rhino-conjunctivitis (rhinoconj.) and of asthma at 5 years of age according to different risk constellations: PA, parental atopy, – none/ + + both parents; AD, atopic dermatitis in first 3 months of life, – no, + yes. Data from the MAS-90-study (Bergmann et al., 1994).

ies should be recommended an indoor allergen avoidance regimen (mite, cat, dog); otherwise, 70% of them will be expected to become sensitized against indoor allergens.

The risk of aeroallergen sensitization at 5 years of age was 67% in children egg-sensitized at 1 and 2 years of age, compared to 47% in children with egg-sensitization at either 1 or 2 years (Kulig et al., 1997). Taking also into account family history increased the positive predictive value for aeroallergen sensitization to 80%, while the risk for clinical manifestation of asthma and rhinitis from these predictors was still only 45 and 48%, respectively (Kulig et al., 1997).

Without laboratory tests, we can predict that 49% of infants who have atopic dermatitis in the first 3 months of life (Bergmann et al., 1994) will develop pollen sensitization by 5 years of age (OR 3.8, 95% CI 1.9–7.4). With two atopic parents, the positive predictive value rises to 71% (OR 9.4, 95% CI 48.9) (Fig. 3). But the risk of developing rhino-conjunctivitis and asthma at this age with the latter risk constellation is still no higher than 37 and 26%, respectively. While the prediction for succeeding atopic disorders from previous symptoms and signs increases with a more rigid definition of the group at risk, the absolute number of individuals at risk decreases, i.e. the mesh of our sieve is getting tighter.

Future research should be aimed at finding more precise predictors for food allergy, as well as for aeroallergy to make possible appropriate preventive measures at the right time. Hopefully, the natural course of atopic diseases will then be ameliorated.

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