

Risk factors in early childhood for the development of atopic diseases

Björkstén B. Risk factors in early childhood for the development of atopic diseases.

Allergy 1994; 49: 400–407. © Munksgaard 1994.

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Accepted for publication 1 January 1994

Several epidemiologic studies in recent years have indicated that the prevalence of allergic diseases is increasing, at least in children and young adults (17, 92, 93). There is increasing experimental and clinical evidence that the conditions under which an allergen is encountered in infancy may have consequences for many years, perhaps even for life (6, 9). If this is true, the prevalence in adults would continue to increase for many years, even after institution of effective allergy-preventive measures in childhood.

The cause of allergy is multifactorial, and depends on the interaction, in genetically susceptible persons, between the time and amount of allergen exposure and the presence of nonspecific “adjuvant” factors, including air pollution (Fig. 1). Environmental factors that influence the development of allergic disease are either specific or nonspecific. To develop an allergy, a person obviously has to be exposed to the allergen. Allergens are present in almost every part of the world, but the relative importance of individual allergens varies, depending on climatic conditions. In subarctic regions, such as Scandinavia, house-dust mites used to be absent, but there is now evidence for their increasing prevalence (61, 85). This may, at least partly, be due to modern building materials and energy-conservation measures (60, 84).

It has usually been assumed that air pollution primarily occurs outdoors. A number of studies have, however, shown that indoor concentrations of some pollutants may be far in excess of the outdoor concentrations (59, 86). There is probably no air out-

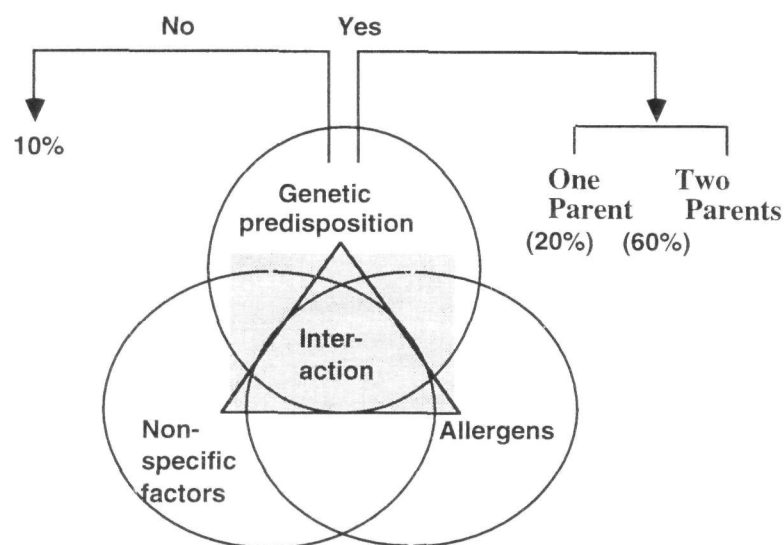


Fig. 1. Schematic depiction of interaction among allergen exposure, nonspecific “adjuvant” factors, and genetic predisposition.

doors as polluted as that in a room where people are smoking. In many countries, outdoor air pollution has decreased over the past decades. Furthermore, there is no clear relation between air pollution and the prevalence of allergy. On the contrary, studies in Sweden have reported a higher prevalence of allergy in the northern, less polluted part of the country than in the southern, more industrialized parts, which are also more affected by pollution from central Europe (92, 93). Therefore, the indoor environment probably plays as large, if not a larger, role in the development of allergic sensitization and the appearance of allergic disease in the sensitized person.

This review discusses various risk factors encountered in early childhood that may influence the development of allergic disease. Some aspects of IgE

regulation will also be mentioned, because this is important for the understanding of the primary sensitization. Evidence will be given for the existence of a period in early life during which either tolerance is induced or a process leading to sensitization is started that may result in manifestations of allergy several years later.

Variations in susceptibility

The relative risk of allergic disease and the tendency to develop allergic disease early in life are both strongly influenced by genetic factors and a family history of allergic disease. The inheritance of atopy is, however, not fully understood. A recent report (21, 87) that atopy and excessive IgE antibody formation are associated with a gene on the short arm on chromosome 11 has not been confirmed (2, 43, 52, 68). Because atopy is associated with several biochemical and immunologic aberrations that could explain parts of the phenotypic expression of allergy, it is perhaps not even reasonable to expect a simple inheritance involving only one or a few genes.

There are a number of immunochemical, biochemical, and clinical tests for identification of subjects at high risk of developing allergy (reviewed in 49). They include family history (47), determination of total (23) and specific IgE (36, 37, 40), and IgG-anti-IgE antibody complexes (79) in serum, skin prick tests (76, 77), lymphocyte tests (7, 8, 19), amniotic fluid analysis (73), leukocyte phosphodiesterase levels (42, 64), basophil releasability (56), and other nonspecific findings such as blood eosinophil counts (27). Unfortunately, none of the procedures for allergy prediction have both a satisfactory sensitivity and specificity. Furthermore, some of the tests are complicated and poorly standardized, and therefore they are not useful in clinical routine. Presently, the most reliable predictive test for future allergy is the detection of IgE antibodies in a clinically healthy infant, either by skin prick tests or in serum.

In addition to genetic propensity, the likelihood of sensitization is affected by the time for, and the conditions under which, exposure to allergens takes place. There seems to be a period in early life during which an infant is particularly susceptible to sensitization. A higher than average incidence of allergy to birch and grass pollen has thus been reported in Finnish schoolchildren born in the spring (10, 11). A similar increase of grass allergy has been reported in British children born in the spring (58), as well as in the prevalence of ragweed allergy in Americans born in the late summer. This relationship between season of birth and development of allergy seems to be limited to children with a congenital propensity for allergy (22). Similarly, early contact with pets and ani-

mal epithelia (74, 82) and house-dust mites (72, 82) and early ingestion of foreign proteins (4) all appear to be associated with an increased risk of allergic disease. A high concentration of an allergen in the home of a neonate, particularly if there is a family history of allergy, may thus increase the prevalence of allergy to that allergen several years later.

Variations in individual susceptibility to sensitization over time may also partly be explained by respiratory tract infection, because sensitization occurs more easily during an infection (28).

Primary sensitization to allergens

Exposure to an antigen is necessary to induce IgE antibody formation. The general tendency to IgE synthesis, as well as the responsiveness to the particular antigen, is enhanced by various nonspecific "adjuvant" factors, including exposure to various air pollutants (Table 1).

A characteristic of IgE antibody formation in animal models is that only extremely low doses of antigen are needed for sensitization (1). Similarly, only minute amounts of antigen are needed to induce an IgE response and to trigger an allergic reaction in man. For example, maternal ingestion of antigenic foods may pass into the breast milk and sensitize the nursing baby (32). The concentrations of antigen are in the picogram–nanogram range per liter milk (26). Once sensitization has occurred, there is a wide variation in sensitivity; the antigen dose needed to elicit symptoms in a less sensitive person is about 1 million times that needed for a highly sensitive person (25).

Temporary formation of IgE antibodies is part of the normal immune response to many antigens. Animal experiments indicate that this response is followed by suppression of the responsiveness and by the induction of tolerance. In a series of ingenious experiments, Holt and coworkers have shown that baby rats, but not adult animals, exposed to an allergen exhibit an IgE antibody response (45, 54, 70). When the animals are reexposed, rat pups of a strain

Table 1. Adjuvant factors believed to be involved in either sensitization, manifestation of allergic disease, or both

Air pollution and sources
Tobacco smoke
Industrial and traffic pollution: solid particles, SO ₂ , NO _x
Combustion byproducts: CO ₂ , CO, SO ₂ , NO ₂ , NO; formaldehyde; volatile vapors
Photochemical reactions; ozone; NO ₂
Building materials; formaldehyde; decoration and paint; solvents; furnishings
Tight, poorly ventilated homes
Pesticides and consumer products; organic substances; aerosols
Respiratory tract infection: viral, pertussis
Vaccines: aluminum?, pertussis?
Ongoing allergic reaction (facilitates sensitization to new allergens)

with a low propensity for IgE antibody formation are "tolerized" and never again respond with IgE antibody formation against that particular allergen. On the other hand, in rats of a strain with a high propensity for IgE antibody formation, the IgE antibody is boosted by repeated exposure to the allergen. Further studies have revealed that in normal, low-responder rat pups the antigen-specific T helper cells are of the TH₁-phenotype, while the predominant antigen response in the high-responder rats is of the TH₂-phenotype. Much higher doses of antigen are needed to induce tolerance in pups of the high- than the low-responder genotype. The differences are up to 10 000-fold; i.e., the low responders tolerate with doses down to the low nanogram level, whereas high responders require up to the high microgram level. It has also been shown to be possible to induce TH₂ responses in low responders by exposing them to certain environmental factors, e.g., histamine and tobacco smoke, thereby demonstrating environmental influence on tolerance induction.

For obvious reasons, less is known of primary sensitization in man. So far, however, data from clinical studies indicate that the process is similar to that in young rodents. A temporary IgE antibody formation is commonly seen against cow's milk and hen's egg during the first year of life (36). In non-atopic infants, the antibody response is short and the levels are low. In contrast, infants who develop allergic disease during the first 7 years of life, i.e., those who are atopic, have a longer lasting response, and the IgE antibody levels are higher (37). Similarly, a temporary, low-level IgE antibody response to inhalant allergens is commonly seen in healthy infants, usually at 2–4 years of age (40). On the other hand, children with high levels of IgE antibodies against inhalants at that age all developed respiratory allergy within the next few years.

Several conclusions can be drawn from the animal and clinical studies. First, the difference between atopic and nonatopic children is not qualitative but quantitative, in that IgE antibody formation against newly encountered antigens is seen in early childhood in both atopic and nonatopic children, although the levels are different. Second, the predominant route of sensitization varies with age. In infants, food antigens predominate as allergens, while inhalants predominate as sensitizing agents after the first year of life. The causes of this age difference are unknown. Possibly, the immune response to inhalants needs to be boosted several times. Third, the major difference between atopic and nonatopic children may lie in different capacity to induce tolerance, as in the differences between young rodents of the high- and low-responder genotypes. The existence of similar mechanisms in human infants is further supported by recent observations of low production of

interferon-gamma (IFN- γ) by cord-blood cells from babies with a family history of atopy (69), of elevated serum levels of IL-4 in infants who later in life develop atopic disease (14), and of delayed maturation of T-cell function (44). The duration of this period in early life during which tolerance is easily induced is not known.

Nonspecific, environmental factors, "adjuvants"

Various environmental factors may enhance sensitization and also trigger an allergic reaction in a sensitized person (Table 1; Fig. 1). While allergy is rare to most of the compounds listed in Table 1, they do play a role in both the sensitization process and the appearance of clinical symptoms. It is not entirely clear exactly how these adjuvants act. Possibly, an inflammatory reaction is induced in the airways that facilitates the penetration of allergens, or, alternatively, enhances antigen presentation.

Three studies of children belonging to the same ethnic group, but living under different conditions, clearly show that the incidence of allergic disease is higher in industrialized countries than in rural areas of developing countries (3, 78, 81). Such environmental differences are also present in industrialized countries, i.e., between urban and rural areas. For example, the relative risk of a positive skin prick test is 70% higher among 11-year-old children living in a moderately polluted town in northern Sweden than among children living in the neighboring countryside (15, 16).

An understanding of the role of environmental factors has been complicated by some recent observations. Air pollution is a major problem in many formerly socialist countries in central and eastern Europe. Yet, the prevalence of atopy among children is much lower than in western Europe. For example, the prevalence of positive skin prick tests in Leipzig in the former East Germany is less than half of that among children of the same age living in Munich in the former West Germany (80). Similarly, atopic sensitization is much lower in Konin in central Poland and in Estonia than in northern Sweden (15). Like the observed differences in skin-prick-test positivity between an urban and a rural area of Sweden, the prevalence of at least one positive skin prick test was significantly higher in Tallinn, Estonia, an industrialized coastal city, than in Tartu, an inland university town in Estonia (Table 2). Thus, although air pollution does seem to play a role in the development of atopy, other factors connected with the Western lifestyle are much more important. The nature of these factors is unknown.

Passive smoking is by far the most documented risk factor for the development of allergic disease.

Table 2. Prevalence of positive skin prick tests (SPT) among 11–12-year-old school-children in five locations in Baltic region (15, 68a)

	Sundsvall, Sweden		Poland Konin	Estonia Tallinn	Tartu
	Rural	Urban			
n=	289	351	358	597	637
≥ 1 positive SPT (%)	24.2	35.3	13.7	12.9	8.3
Crude odds ratio	1	1.71	0.49	0.46	0.28
95% CI		1.2–2.4	0.3–0.7	0.3–0.7	0.2–0.4

This is particularly true in early childhood, independently of how “allergy” is defined. Numerous epidemiologic studies have found an association between exposure to tobacco smoke and recurrent wheezing (20), bronchial hyperreactivity, and the diagnosis of asthma (48, 62, 63, 75). An association between passive smoking and an increased risk of sensitization to environmental allergens has also been shown, in both clinical studies (65, 91) and animal experiments (90). There is little doubt that exposure to tobacco smoke is the most important environmental risk factor for childhood allergy and respiratory disease identified so far. The long-term effects of childhood exposure to tobacco smoke are unknown.

In addition to the introduction of many new chemicals in the environment, there have been many changes in lifestyle in industrialized countries over the past few decades. The type of foods eaten has been changed dramatically by the introduction of new products with numerous additives. Even fresh foods differ much from those of only a few decades ago. For example, by genetic manipulation and use of various chemical compounds, the storage time of food has been much prolonged; for example, apples may have a shelf life of months. Virtually nothing is known of the possible influence on childhood allergy of such changes in the diet.

Psychologic factors may also influence the immune system. For example, family interaction is often disturbed in the families of asthmatic children, and family therapy improves the asthma (34, 35). A recent prospective study investigated whether the disturbed family’s interaction is a primary finding or a consequence of disease (33). The study included the families of 100 infants with a strong family history of allergy. The entire family participated in a standardized family test when the children were 3 and 18 months old, assessing ability to adjust to demands of the situation (“adaptability”) and the balance between emotional closeness and distance (“cohesion”). An unbalanced family interplay was common at 3 months (37%), but it was not predictive of respiratory illness. At 18 months, a dysfunctional interaction was significantly more common in families of children with eczema and obstructive

symptoms than in families of healthy children. The study indicates that a dysfunctional family interaction is the result, rather than a cause, of recurrent wheezing in infancy.

The role of infections, notably in the respiratory tract, as risk factors for the development of childhood allergic disease is complex. An infection induces an inflammatory reaction in the respiratory mucosa, which in turn modifies the local immune response. To what extent this enhances sensitization to inhaled allergens is not fully known, although there are studies indicating that this is so for infection by at least some viruses, notably respiratory syncytial virus (83). Animal experiments support the clinical observations, showing enhanced IgE production after allergen exposure and concomitant viral infection (70). It is also known that infections may trigger clinical symptoms in already sensitized patients, and that infections increase bronchial hyperreactivity.

Among the infectious agents, *Bordetella pertussis* is of particular interest, because it is a well-established adjuvant for the induction of IgE antibody formation in experimental animals (67). Furthermore, whooping cough is associated with bronchial hyperreactivity for several months (71). It has also been shown that IgE antibodies against pertussis toxin appear after an infection (41) and after immunization against pertussis (13). The latter observation suggests that vaccinations may be a risk factor for allergic disease. This notion is further strengthened by the fact that aluminum, which is used as an adjuvant in many vaccines, is also one of the most potent adjuvants for IgE antibody synthesis in animals (12). Properly designed epidemiologic studies are needed to clarify a possible relation between routine immunizations of infants and development of atopic disease.

Pre- and perinatal risk factors

Because some neonates who will develop allergic disease can be identified at birth by an elevated level of IgE in cord blood, it has been suggested that sensitization may take place during fetal life. However, this occurs rarely. The IgE in cord serum seems to be more the consequence of nonspecific spontaneous IgE synthesis, perhaps lack of suppression, than of antigen stimulation. This notion would be supported by the negative outcome of randomized studies of manipulation of the maternal diet during pregnancy (29–31, 50, 51, 88, 89). On the other hand, some recent studies recorded antigen-specific T-cell responses in cord blood. However, these studies did not control for several alternative possibilities, and they are therefore not conclusive. The possible role of intrauterine sensitization therefore remains undetermined.

It has also been suggested that perinatal stress factors can increase the risk of later allergic disease. However, these studies (summarized in 9) were retrospective, and did not control for various other possibilities. In unpublished studies, we have not seen any indication that prematurity is a risk factor for atopic sensitization.

While there is convincing evidence of an association between exposure to tobacco smoke and childhood allergy, the role of smoking during pregnancy is less clear. Although there are reports of an association between maternal smoking and childhood allergy, the studies are inconclusive because of their design (53). Infants of smoking mothers are, however, exposed to significant amounts of nicotine in breast milk (24).

Medication with the β -receptor blocking agent propranolol during the first trimester of pregnancy has been reported to be associated with an increased risk of allergy in the children (5). This observation is interesting because β -receptor blockade may enhance IgE antibody formation in animals (46, 66).

Progesterone given for various reasons to pregnant women has also been reported to be associated with increased levels of IgE in cord blood (57). This study has not been published in full, nor has the observation been confirmed in other studies.

Infant feeding

A great interest has been taken over the past 10 years in the possibility of preventing allergic disease, notably asthma, by avoiding primary sensitization in early life. The efforts have been focused on various allergen-avoidance procedures, including administration of infant formulas with reduced allergen content.

The original hypothesis of the allergy-preventive efforts was that allergic disease could be avoided by preventing the onset of the "allergic march" in early infancy. Thus, by preventing the development of food allergy and eczema in early life, the later onset of asthma and then allergic rhinoconjunctivitis would be avoided. Recent prospective studies of infants with a genetic predisposition to allergic disease have not confirmed this hypothesis. In these studies, exposure of infants to allergenic foods during the first months of life, notably cow's milk and hen's egg, was avoided (18, 38, 39, 88, 89). The mothers of breast-fed babies adhered to a diet free from cow's milk, hen's egg, and certain other allergenic foods, and any supplementary feeding of the babies was in the form of extensively hydrolyzed products with low allergenicity. The dietary manipulation of breast-feeding mothers and infants was associated with a lower incidence of allergic manifestations and detectable IgE antibodies against foods. However, the effect

was limited to the first year, or possibly first 2 years, of life and to eczema, while the incidence of respiratory symptoms and later allergic manifestations was not affected. The results are not surprising in light of the more recent knowledge of the primary sensitization discussed above. The experimental studies clearly indicate that the effects of avoidance of exposure to allergens during the period of particular susceptibility in early life is antigen specific (45, 55). Thus, dietary restrictions would not be expected to have an effect on sensitization to inhaled allergens, nor to reduce the incidence of sensitization to food antigens not avoided. The practical conclusion is that the various "hypoallergenic" infant formulas, some of which should not even be regarded as "hypoallergenic", do not represent a major improvement in the search for effective allergy prevention. At best, they might reduce the incidence of cow's milk allergy in infants, provided truly hypoallergenic preparations are used. To avoid sensitization to other allergens, a person must avoid each of them. Thus, for prevention of allergic asthma, either all important inhalant allergens must be avoided, or adjuvants for sensitization must be avoided. Neither of these is easily achieved.

Conclusions

Although not conclusively proven, it is reasonable to assume that the prevalence of atopic disease has increased over the past decades. It is also reasonable to suggest that this increase is largely a consequence of changes in the environment that one is exposed to early in life, because there seems to be a period during which the primary sensitization takes place that results in allergic manifestations later in life. Although environmental factors undoubtedly play a major role in the development of allergic disease, the mechanisms, as well as the individual factors, are unknown. Recent studies in formerly socialist countries of Europe, where lifestyle in many respects is similar to that of Western Europe 30–40 years ago, lend strong support to the notion that the prevalence of allergy has increased. Whether the Western lifestyle is associated with an introduction of new, unknown adjuvants enhancing sensitization, or whether factors that are necessary for the induction of tolerance are absent is not known. Efforts during infancy to effect primary long-term prevention of allergic disease have largely failed and are probably based on an incorrect hypothesis. Thus, it seems likely that avoidance of exposure to allergens is antigen specific, and avoidance of, say, allergenic foods in infancy would result only in less allergy to that particular food, and not in any reduction of, say, allergy to inhaled allergens.

The only definite measure to reduce the general

risk of allergy and asthma is carefully to avoid all exposure of infants and young children to tobacco smoke. In addition, avoidance of certain allergens for the first years of life may reduce the incidence of sensitization to that particular antigen. However, there is very little evidence that such avoidance would reduce the general propensity to allergy. The pathogenesis of atopic sensitization and development of allergic manifestations remains an enigma, although there is much circumstantial evidence that the process starts during early childhood, even if clinical symptoms do not appear until later in life.

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