

Natural course of asthma and allergy in childhood

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Asthma, allergic rhinitis, atopic eczema and other diseases where allergic manifestations play an important role (1) are increasingly common in infants and children (2, 3). The development is under genetic control (4–6). A change in the genetic code can hardly explain the rapid increase in allergy during the past 30 years. Indoor and outdoor environmental factors, i.e. allergens and “irritants”, e.g. tobacco smoke, acting in concert, are likely to underlie the increase in allergic reactions (3, 7).

Nowadays, one child in three has experienced at least one allergic manifestation before 11 years of age. Asthma is the most common chronic disease in childhood. Yet, asthma is under-diagnosed and under-treated, leading to unnecessary suffering and many days off school (8, 9). There are also occasional deaths from asthma or anaphylaxis due to food allergy, some of which should have been avoidable (10, 11). Hence, there is great need for further increase in the knowledge about factors affecting the development, the severity and day-to-day situation, and the prognosis of asthma and other allergic diseases. Our present knowledge should be made available not only to patients and their families, but also to e.g. all medical personnel and personnel at day-care centres and schools. Decision makers should be aware of the impact of allergic diseases and act to improve the situation for those already sick and, even more important, institute measures to prevent development of new allergies.

Development of sensitization/allergy

Genetic factors

The genetic background is complex but progress has been made during the last years (4–6, 12). Polygenic influence seems to explain the development better than variations at a single locus as we have to explain genetic influence on the risk for development

of any atopic manifestation, end organ sensitivity, hyperreactivity, total IgE level and specific sensitization. In about 3% of newborn infants, the family history is bilateral which indicates a very high risk for allergic disease (13). The highest risk for any atopic manifestation (60–80%) is found in babies of parents suffering from identical allergic manifestation, e.g. bronchial asthma (14). The risk for cow's milk allergy in subsequent children, when there is already a child with it in the family, was estimated to 1: 3 (15). Boys tend to have an earlier onset of allergic disease than girls. Allergic manifestations start at an earlier age when there is a family history of allergy, especially when both parents suffer from allergic manifestations (16).

Breast feeding and other preventive measures appear especially important for delaying symptoms and signs of allergy in “at risk babies”, i.e. when there is a family history of allergy/atopic disease (17, 18) or a high cord blood IgE concentration (17).

Sensitization to allergens

Proteins or gluco-proteins with a wide range of molecular weight (5000–75000) may act as allergens and induce sensitization. The age and previous immunological experiences of the subject are important for the outcome of ingestion or inhalation of allergens (19). There is a period of enhanced susceptibility to sensitization in early infancy. The response to an allergen is also influenced by maternal immunity during the first months of life (20). This influence is exerted by trans-placental transfer of e.g. immunoglobulins and by various components of breast milk (21, 22). Often, there is interaction between several risk factors behind sensitization and eliciting of symptoms and signs of allergy. Ongoing allergic or other inflammation enhances further sensitization.

Only few cases of verified (food) sensitization in utero have been published (20). Maternal food intake during pregnancy seems to have little influence on subsequent allergy. Transient food sensitization is common in babies with no allergic symptoms (23) but it is even more common in babies at high risk for allergy (24). Human neonates seem especially prone to food sensitization, e.g. to cow's milk (25). Cow's milk formula given as one or two meals at the maternity ward seems to be an important cause of cow's milk hypersensitivity. Food allergy often develops as the first evidence of a genetic predisposition towards the development of atopic disease (26–30).

There are apparently differences in breast milk quality through variation in the content of protective and allergy promoting factors. Food sensitization may occur through minute amounts of allergenic food residues from maternal food intake in the breast milk (18, 29, 31–35). Maternal diet during lactation transiently reduced food sensitization and atopic eczema (28, 36). Maternal dietary restrictions during late pregnancy and throughout lactation, combined with late introduction of allergenic foods to the baby, gave a threefold reduction in food associated atopic dermatitis, hives and/or gastrointestinal disease in the first 12 months, but later the prevalence was not influenced (26). A difference in positive skin prick tests was due primarily to a higher prevalence of sensitization to cow's milk (12% in the control group versus 1% in the prevention group). The development of allergic rhinitis and asthma up to 4 years of age was, however, not influenced by diet. The period prevalence of food allergy was similar in both groups at 4 years of age.

Early introduction of highly allergenic foods into the diet of high risk babies is a risk factor for food allergy/allergic disease while late introduction of all allergenic foods, in addition to breast feeding for 6 months or more, delayed the onset of food allergy and atopic eczema (37).

Season of birth is important for the development of disease and sensitization: the risk for pollen sensitization is greatest in babies born during the spring, while sensitization to mites and pet animals is over-represented among those born during the autumn/winter seasons (38–41). Keeping a pet during the first year of life increases the risk for pet sensitization as compared to keeping a pet later on (42, 43). The rate of mite sensitization depends on mite concentrations in the environment, especially in bedroom and mattress dust (44–47).

Irritants/adjuvants

A lot has been written lately about the probable influence of environmental factors acting as adju-

vants for sensitization and symptoms of allergy. However, although there is proof for adjuvant effects in animal experiments, less is really known regarding the effect of various environmental factors acting as adjuvants in man (48–55). It is well established that maternal smoking increases the risk for allergic symptoms during infancy and early childhood (34, 50, 56–61). Infections precipitate symptoms of asthma in predisposed infants and children, but there is some doubt about their role as inducers of allergy and asthma. Little is actually known about non-allergenic indoor and outdoor factors as inducers of allergy and asthma but epidemiological studies point to the importance of indoor humidity and outdoor pollution from e.g. paper pulp factories (57). The "modern way of living" includes several factors which alone or taken together may affect the risk for development of allergy and atopic disease. Modern houses are well insulated and tight. Material used for the construction is selected for practicality and often causes emission of various chemicals with unknown effects on human beings. Ventilation is often insufficient or may even add to indoor pollution. Many buildings are thus now classified as sick (62). Activities including the use of gas stoves may contribute to respiratory symptoms (53). Ozone may contribute to bronchial hyperreactivity (48).

Development of atopic disease

Atopic eczema

Atopic eczema is characterised by dry, itchy skin and typical localisation of erythema, scaling and scratches. Ten percent of children or more suffer from atopic eczema during a significant period during their first 10 years (63, 64). The onset of symptoms is usually in infancy. Lately, we and others have found that many cases of eczema also may have a later onset (64, 65). The development of eczema is highly influenced by genetic and dietary factors as previously discussed but also environmental factors have been blamed (32, 35, 66).

Allergic rhinitis

Occasionally, allergic rhinitis may be seen in infants but it becomes more common with increasing age (13, 57, 64, 67). 10–15% of teenagers suffer from allergic rhinitis (7, 64). Perennial allergic rhinitis, mostly due to allergy to pet animals and/or mites, tends to start at an earlier age than seasonal allergic rhinitis due to pollen. Pollen allergy, especially birch pollen allergy, is often accompanied by oral itch and swelling of mucous membranes when eating certain foods. Birch pollen-associated foods are nuts, apples and peaches. A history of birch pollen-associated oral symptoms when eating an apple is increasingly

often found with increasing severity of allergic rhinitis. There is no general agreement as to the risk for later asthma in those suffering from allergic rhinitis, but often figures round 50% are mentioned. The prevalence of allergic rhinitis in asthmatics increases with asthma severity (68).

Asthma

Wheezing is reported from about 20% of all infants once or more during respiratory tract infections. Certainly not all of these develop asthma. Risk factors for asthma include a family history of allergic disease, especially bronchial asthma, exposure to environmental tobacco smoke and indoor pets. Having eczema and/or evidence of atopic sensitization highly increases the risk for development of asthma in babies wheezing at respiratory tract infections. In our cohort of 1654 consecutively born children followed from birth, the cumulative incidence of asthma up to 11 years was 5% and the prevalence 3% at 11 years of age (64, 68). Others have reported similar or even higher prevalence in our and other countries, and prevalence rates up to 12% have been reported (3, 69, 70).

Wheezing is the most obvious finding in infants with asthma. In toddlers asthma may start with cough in connection with playing and crying or during nights. Prolonged coughing more than 14 days after a common cold may be regarded as indicating bronchial hyper-responsiveness. In some children establishing of the correct diagnosis is delayed and they have been treated for "bronchitis" and "pneumonia" repeatedly for years before it is realised that they have asthma. It is also relevant to consider an asthma diagnosis in children who have no wheezing, only a history of change from full activity and physical fitness to a "bystander" role when others play e.g. football (8, 68).

The onset of asthma was prior to 1.5 years in 1/3 of our previously mentioned asthmatics and before 3 years in 1/2 of our children (68). This corresponds to the reports by others: 80% develop their disease before 5–7 years of age. Boys tend to start at an earlier age than girls. The development of asthma and other atopic diseases in our cohort was related to the family history of allergy/atopic disease, the season of birth (peaking in August–October) and the neonatal serum IgE concentration in cord blood (CB-IgE). A family history of allergy doubled the risk for asthma but an elevated CB-IgE (≥ 0.9 kU/l) increased the relative risk for asthma by a factor of five.

Factors affecting severity of disease

Atopic eczema

Eczema is usually worsened by infections including those in the upper respiratory tract. Local skin infections and exposure to allergens by ingestion or inhalation are known to worsen the eczema in many children. A dry indoor climate worsens the situation. If it is possible to avoid identified allergens, improvement can be achieved but the skin still needs supporting treatment with emollients. Infants and children with multiple allergies to foods and other manifestations of allergy tend to have a more severe eczema. The correlation between the serum IgE concentration and severity of eczema is poor.

Asthma

Cord-blood IgE concentration and a positive immediate family history of atopic disease had no predictive value for the severity of asthma at follow-up at 12–14 years of age in our study (68). Children with severe asthma as judged from a high total asthma score (based on symptoms, social impact and medication) at 11.5–14.5 years of age had more concomitant allergic diseases, earlier onset of asthma, more chest deformity, hyperreactivity both on tread mill and histamine challenge tests, elevated IgE, positive Phadiatop and more reactions at skin prick test, especially to animals and mites. The severity of the asthma was not influenced by the month of birth. No significant differences were found between boys and girls regarding asthma severity at follow-up or bronchial histamine threshold levels.

Prognosis of allergy and asthma

Food allergies

Most food allergies tend to disappear after a period of months up to decades (27, 30, 71–73). Differences in disappearance rate depend on the allergen and on individual factors in the person subject to the allergy. Most children with cow's milk allergy tolerate at least small amounts of cow's milk at 3 years of age. Similarly, egg allergy tends to subside before 7 years of age while allergy to fish, soy and nuts tends to remain for considerably longer time. Esteban found the computed mean "survival" of food allergy to be 71% after 3 years, 50% after 6 years and 28% 9 years after establishing a diagnosis of food allergy (71). A poorer prognosis for disappearance of egg allergy was found with early start of egg allergy and if the child had more than one atopic disease. A favourable prognosis was found with decreasing skin prick test wheal to egg, with a short duration of

symptoms and in the absence of respiratory symptoms or angioedema.

Eczema

Varying long-term prognosis has been reported for atopic eczema in infancy (74, 75). As already mentioned a considerable proportion of babies outgrow their eczema, but develop respiratory allergy. Eczema in young adults is mostly seen in those with a family history of eczema, if there is concurrent bronchial asthma, and if there was early onset of eczema with severe symptoms during the first years of life. Localisation to the hands during childhood is a risk factor for continuing skin problems. Girls have a poorer prognosis than boys as women with childhood eczema who get a job with much hand washing are highly prone to show eczema in adulthood (76). Many adults with a history of atopic eczema during childhood still show a dry skin, prone to itch at exposure to wool, for example.

Generally, infants with atopic eczema have a 50% risk for later development of respiratory allergy: allergic rhinitis and/or bronchial asthma. There was a three-fold increased risk for allergic rhinitis in eczema subjects with a family history of allergic rhinitis and a doubled risk for asthma when there was a family history of asthma (75, 77). An elevated cord blood IgE concentration doubled the risk for respiratory allergy in infants with eczema (64). The risk for respiratory allergy increased with increasing severity of eczema (75). Boys with eczema developed asthma or rhinitis 3 times more often than girls (75, 77). Low age at debut of the eczema predisposed to respiratory allergy (77, 78). Atopy, defined as positive skin tests (normally to egg during infancy) increased the risk for later sensitization to inhaled allergens and symptoms of respiratory allergy, i.e. asthma or allergic rhinitis (73).

Allergic rhinitis

Most children who start having allergic rhinitis seem to go on having symptoms up to adulthood except the few who are mono-sensitised and avoidance is possible (65). Bronchial asthma is said to develop in about 50% of children suffering from allergic rhinitis.

Wheezing

Generally, the prognosis is good for infants who only wheeze during a few respiratory tract infections. If the episodes are severe or if there is wheezing or cough also between infections or other manifestations of atopic disease the prognosis is poorer (68, 77, 79–83).

Asthma

The prognosis of asthma is poorer, if the child has had severe asthma in childhood and/or concurrent allergic disease. Furthermore, the prognosis is poorer if the child has IgE-mediated allergy or a family history of asthma. Similarly, it is poorer if there is a chest deformity or severe bronchial hyper-reactivity. Elimination of environmental exposure to tobacco smoke, furred pets and mites is vital for the long-term prognosis. About 50% of asthmatics are symptom free about 20 years after the diagnosis has been established, but many of them still show bronchial hyperreactivity and at least 25% of them will get back symptoms within years or decades. The working capacity is normal in asymptomatic asthmatics but there is still evidence of disturbed ventilation/perfusion (81). Also asymptomatic cases tend to have a more rapid decline in lung function with age, thus emphasising the importance of early and intense treatment of the disease in childhood.

Conclusions

Asthma and other allergic diseases have multifactorial background both at sensitization, acute and chronic symptomatic stages. Allergens and adjuvants interact with genetic factors. Previous experience and current degree of inflammation are important for the response at each exposure. Multidisciplinary efforts and massive education are needed to bring the ongoing increase of these diseases to an end. Genetic studies in well defined groups of patients may give means to identify babies at particularly high risk for allergy and asthma. Prevention of onset of symptomatic asthma should be the goal for us for the year 2000.

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