Primary Prevention of Atopy

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46.1 Introduction and Definition

Atopic diseases such as hay fever, asthma, and eczema are allergic conditions that tend to cluster in families and are associated with the production of specific IgE antibodies to common environmental allergens. The process of sensitization may or may not be associated with the induction of clinical symptoms, which by themselves are characterized by inflammation, corresponding to hyperresponsiveness of skin or mucosal membranes.

The term “atopic march” refers to the natural history of atopic manifestations, which are characterized by a typical sequence of IgE antibody responses and clinical symptoms that appear during a certain age period, persist over years and decades, and often show a tendency for spontaneous remission with age.

In order to identify potential modifiable determinants, cross-sectional as well as longitudinal epidemiological studies on the development of atopic diseases have received much attention over the past decade [1, 2]. The number of intervention studies [3], which provide the most useful information, is still limited. It is obvious that a prerequisite for any intervention aiming at the prevention of atopic manifestations is the identification of nongenetic determinants such as exposure to environmental factors, food, or lifestyle related factors, which are modifiable on an individual basis or as a result of public health measures.

46.2 The Natural History of Atopic Manifestations

During the first months of life, the first IgE responses directed to food proteins may be observed, particularly to hen’s egg and cow’s milk. Even in completely breast-fed infants, high amounts of specific serum IgE antibodies to hen’s egg can be detected. It has been proposed that exposure to hen’s egg proteins occurs via mother’s milk, but this needs further clarification [4–6].

Sensitization to environmental allergens from indoor and outdoor sources requires more time and is generally observed between the 1st and 10th year of life (Fig. 46.1). The annual incidence of early sensitization depends on the amount of exposure. In a longitudinal birth cohort study in Germany (MAS) a dose-response relationship could be shown between early exposure to cat and mite allergens and the risk of sensitization during the first years of life.

It has recently been demonstrated that strong infantile IgE antibody responses to food proteins have to be considered as markers for atopic reactivity in general and are predictors of subsequent sensitization to aeroallergens.

As far as clinical symptoms are concerned, atopic dermatitis in general is the first manifestation, with the highest incidence during the first 3 months of life and the highest period prevalence during the first 3 years of life.

Fig. 46.1. Development of atopic manifestations in the first 10 years of life, observed in a German birth cohort.
Seasonal allergic rhinoconjunctivitis is generally not observed during the first 2 years of life, although a minority of children will develop specific IgE antibodies during this early period. Obviously, two seasons of pollen allergen exposure are required before a classical seasonal allergic rhinoconjunctivitis with typical symptoms in association with specific serum IgE antibodies becomes manifest. Prevalence before the end of the first decade in children is around 15% in central Europe.

Asthmatic wheezing may already be observed during early infancy. The majority of early wheezers turn out to be transiently symptomatic, whereas a minority may persist throughout school age and adolescence. Still, our understanding of the natural history of childhood asthma is limited, and numerous data sets support the existence of various asthma subtypes in childhood. During the first 3 years of life, the manifestation of wheeze is not related to elevated serum IgE levels or specific sensitization, and a positive parental history of atopy and asthma seems to be of minor importance during the first 2 years of life. Those who have persistent wheezing show an association with early sensitization to food and subsequent sensitization to aeroallergens. In addition, the association with a positive family history for atopy and asthma in first-degree relatives becomes more and more obvious [7].

### 46.3 Hereditary Factors

It has been known for many years that atopic diseases run in families. The risk for neonates of developing atopic symptoms during the first two decades of life strongly depends on the manifestation of the disease in their parents and siblings. Already at the phenotype level, it is obvious that there is a closer association between specific symptoms such as asthma or atopic dermatitis in the child and the same manifestation in parents or siblings than with other atopic manifestations in the family. These clinical observations already suggest the presence of phenotype-specific genes.

During the last two decades, molecular genetic studies have been performed for various allergic diseases including asthma. Two approaches are being applied in order to identify genes related to disease:

1. Positional cloning in which the entire genome is screened using a panel of polymorphic DNA markers. This approach attempts to demonstrate a genetic linkage of a certain phenotype and genetic markers of known chromosomal localization (Fig. 46.2).

2. Examination of candidate genes already known to be involved in the pathophysiology contributing to a certain phenotype. The role of candidate genes may be assessed by defining polymorphisms within the respective genes and testing for associations with the disease.

To date, a variety of markers on specific chromosomal regions have been found to be linked to either atopic dermatitis or asthma, whereas other regions seem to be linked to several atopic phenotypes. If genetic studies turn out to be fruitful, they might contribute to the identification of candidates for primary prevention measures, and individuals who may respond to certain therapeutic interventions in the future [8–12].

![Fig. 46.2. Loci for atopic eczema in three genome-wide linkage studies](image-url)