

Development of atopic sensitization and allergic diseases in early childhood

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Atopic diseases and atopic sensitization were studied from birth up to 2 y in a population-based prospective study. Physical examinations were done at 6, 12 and 24 mo, including skin-prick tests and blood samples, for the determination of serum IgE level and circulating IgE antibodies to food and inhalant allergens. In addition, questionnaire surveys were done about clinical symptoms of allergy, infections and the home environment. At 2 y the prevalences of definite and probable atopic diseases were 17% and 13%, respectively. The cumulative incidence of allergy was 25%. Atopic dermatitis was the main manifestation of atopy, with a peak prevalence of 15% at 2 y. The prevalence of positive skin-prick tests was constant at all ages, i.e. 7% at 6, 12 and 24 mo. Positive skin-prick tests against inhaled allergens were more than twice as common at 24 than at 12 mo, while sensitivity to food decreased. In contrast, circulating IgE antibodies to egg became more common with age, reaching 20% at 2 y.

Conclusions: The present study indicates that manifestations of allergic diseases and incidence of sensitization to foods and inhalants are equally common in Estonian and Scandinavian children during the first 2 y of life, despite a much lower prevalence among older children and adults in Estonia.

Key words: *Atopic diseases, atopic sensitization, early childhood*

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Epidemiological studies over the last 7 y have demonstrated a low rate of atopic sensitization, hay fever and asthma in children in the former socialist countries of Central and Eastern Europe compared with Western Europe (1–5), while recurrent infections appear to be more common (3, 4). Thus, environmental factors associated with a western lifestyle seem to be of major significance for the high prevalence of allergy in countries with a market economy.

It is well known that environmental factors in early childhood influence the appearance of allergic manifestations later in life, and there seems to be a period early in life during which primary sensitization takes place (6). In a recent study we showed that the incidence of allergy and atopic sensitization among Estonian infants (7) is not as low as could be expected from the low prevalence in older children and adults (4, 8). This could possibly indicate that the western lifestyle introduced in Estonia after regaining independence in 1991 had already affected the infant population. Another possible explanation, based on animal experiments (9) and clinical observations (10), would be that temporary sensitization is common in early childhood

and then under normal circumstances is followed by the down-regulation of IgE antibody responses. If this is the case, then this down-regulation might eventually be more effective in Estonia and other countries of Eastern Europe than in countries with a high prevalence of allergy. We therefore conducted a prospective study to assess this possibility. The present study focuses on the development of atopic sensitization and atopy related diseases up to 2 y of age.

Material and methods

Study population

The initial study population comprised 298 healthy, newborn babies born at term at the Women's Clinic of Tartu University during a 4-mo period from November 1993 to February 1994; the parents agreed to participate in the study. The study population and the study design have been described in detail elsewhere (7). Briefly, the children were subject to a follow-up at 6, 12 and 24 mo. This included a physical examination by one of us (MV and KJ), questionnaires, skin-prick tests (SPT) and

determination of circulating IgE antibodies. The questionnaire included questions related to symptoms of allergy, living conditions and respiratory tract infections. Of the families who initially agreed to participate, 173, 220 and 223 (105 girls, 118 boys) did so at 6, 12 and 24 mo, respectively, and 129 children attended on all the three occasions. The main reasons for dropping out were transportation problems and moving out of town. The family history of atopy, tobacco smoking at home and socio-economic status were, however, similar among the infants who were and were not followed up.

Skin-prick tests

SPT were performed with fresh food allergens (fresh cow's milk, egg white) employing the prick-prick method and with standardized inhaled allergen extracts (Solu-Prick SQ, ALK, Hørsholm, Denmark) of *Dermaphagoides pteronyssinus*, cat and dog dander, birch, timothy and mugwort. The potency of the allergens was 10 histamine equivalent prick units (HEP). Histamine dihydrochloride, 10 mg/ml was used as a positive control. All the prick tests were performed in duplicate by the same nurse in accordance with the instructions of the European Academy of Allergy and Clinical Immunology (11). The SPT was regarded as positive when the mean diameter of one of the wheals was at least 3 mm.

Laboratory analyses

Venous blood samples were drawn into vacutainers. After clotting at room temperature, the samples were centrifuged and sera were frozen and stored at -20°C . Sera from all 129 children, who were studied on all the three occasions, were analysed for the presence of IgE antibodies against egg white, birch, cat and *D. pteronyssinus* by means of a chemiluminescence method according to the recommendations of the manufacturer (Magic Lite, ALK), employing high sensitivity (HS) modification. The detection limit for the test procedure was 0.5 SU/ml, corresponding to approximately 0.09 Paper Rast Units (PRU) in the test system manufactured by Pharmacia (Uppsala, Sweden). Cut-off point for a positive test result was 1.43 SU/ml (1 class). Determination of circulating IgE antibodies against allergens was determined in the Tartu Children's Hospital Immunology Research Laboratory.

Diagnostic criteria

The diagnostic criteria for atopic diseases were the same as described in a previous paper (7) and identical to those used in numerous prospective studies previously conducted in Sweden (12, 13). Briefly, atopic dermatitis was defined as chronic or chronically relapsing dermatitis, as suggested by Hanifin and Rajka 1980 (14), and asthma as three or more separate episodes of wheezing, at least once verified by a doctor. Allergic rhinitis/

conjunctivitis was defined as symptoms appearing at least twice after exposure to a particular allergen and unrelated to infection. The diagnosis of allergic urticaria was based on a history of generalized urticaria, appearing at least twice within 1 h after exposure to a particular allergen. Vomiting and/or diarrhoea on at least two separate occasions after intake of the offending food were considered as gastrointestinal allergy. The term "probable allergy" was used to indicate cases where most but not all the diagnostic criteria above were met. The results of SPT and the levels of IgE antibodies in blood were not taken into account when verifying an allergic disease. A doctor verified diagnoses of otitis, wheezy bronchitis and pneumonia at the time of such illnesses, based on physical examination and X-ray.

Statistical analysis

Analyses were performed using the statistical package SAS Version 6.10. The IgE values were presented as geometric means. The Mann-Whitney test was employed for comparing the S-IgE levels in the various groups of children and χ^2 for comparing the prevalence of positive SPT, circulating IgE antibodies and clinical manifestations of allergy.

Ethical considerations

All parents of the participating children gave signed informed consent. The Medical Research Ethics Committee of Tartu University approved the study.

Results

The point prevalence of atopic diseases increased from 8% at 6 mo to 15% at 12 mo and 17% at 2 y (Table 1), while 23%, 22% and 13% respectively had probable allergy. Atopic dermatitis was the main manifestation of atopy, with a peak prevalence of 15% (35/223) at 2 y. Thirteen of them developed their symptoms during the first year of life and 22 during the second year.

Respiratory allergy appeared mainly after the first year of life. Asthma was present at 24 mo in four children (2%) and allergic rhinoconjunctivitis in two (1%). Wheezing twice or more was reported in 21% of

Table 1. Point prevalence (%) of obvious atopic diseases in the cohort.

Age	6 mo (n = 173)	12 mo (n = 220)	24 mo (n = 223)
Atopic dermatitis (AD)	4	10.5	15
Bronchial asthma (BA)	0	0.5	2
Allergic rhinoconjunctivitis	0	0	1
Gastrointestinal allergy	2	1	1
Urticaria	2	3	0
Any	8	15	17

Table 2. Prevalence of positive skin-prick tests in Estonian children during the first 2 y. Percentage figures are shown within parentheses.

Allergens/age	6 mo (n = 170)	12 mo (n = 220)	24 mo (n = 222)
Cows' milk	3 (2)	2 (1)	0
Hens' egg	9 (5)	9 (4)	4 (2)
Cat	—	3 (1)	9 (4)
Dog	—	1 (0.5)	5 (2)
<i>Dermatophagoides pteronyssinus</i>	—	4 (2)	5 (2)
Birch	—	—	1 (0.5)
Timothy	—	—	0
Mugwort	—	—	0
Any	12 (7)	16 (7)	16 (7)

the children during the first 2 y of life. More than 6 upper respiratory tract infections during the second year of life were reported in 22%, and 21% of children had otitis at least once. Six children (3%) had pneumonia and 4 children (2%) whooping cough during this period. All these diagnoses were verified by a doctor and reported by the parents in the questionnaires. Only three children had symptoms of gastrointestinal allergy during the second year of life and none had urticaria. The cumulative incidence of an obvious allergy was 25% at 2 y, as calculated on the 129 children who attended all three follow-ups. In 14 of the 38 children with atopic manifestations at 2 y, the symptoms continued from infancy, i.e. atopic dermatitis ($n = 11$), gastrointestinal allergy ($n = 2$) and asthma ($n = 1$).

The mean diameter of the histamine-induced wheal in the skin-prick test was 4.4 ± 1.3 mm at 2 y. Sixteen children out of 222 tested children (7%) had a positive skin-prick test to at least one allergen at 2 y (Table 2). Nine of them were sensitized to two or more allergens. The prevalence of positive skin-prick tests was similar at all ages, i.e. 7% at 6 mo, 12 mo and at 2 y. The prevalence of sensitization against inhaled allergens increased from 12 to 24 mo, while sensitivity to food allergens declined.

At 2 y, positive SPT to cat, dog, *D. pteronyssinus* and birch were recorded in 9, 5, 5 and 1 child, respectively. Eight children of 38 with clinically manifest allergy had a positive SPT results compared to only 6/156 healthy children ($p = 0.003$). The corresponding figure in the group with probable allergy was 7% (2/29).

The GM ($\pm$ SD) of S-IgE was different at 24 and 12 mo [19 (3–112) kU/l and 8 (2.0–29) kU/l, respectively, $p < 0.001$]. The mean S-IgE levels were similar in 38 allergic children and 156 non-allergic children, i.e. 18.5 and 16.1 kU/l, respectively, ns.

The prevalence of circulating IgE antibodies to allergens among the 129 children who participated in all three follow-up investigations is given in Table 3. The prevalence of IgE antibodies to cat increased from 3% at 1 y to 11% at 2 y. A striking increase was seen for circulating antibodies to egg from 1 to 2 y of age, i.e. from 5.5% to 20%, while the prevalence of positive

Table 3. Prevalence of circulating IgE antibodies at 6, 12 and 24 mo in the 129 children who attended all three follow-ups.

Allergen	6 mo	12 mo	24 mo
Egg white	5/122	7/126	25/126
Birch	0/122	3/126	5/128
Cat	2/122	4/127	14/129
<i>D. pteronyssinus</i>	0/122	2/126	8/129

skin-prick tests declined from 4% to 2%, as shown in Table 2. There was no close correlation between the SPT results and circulating IgE antibodies, and the discordance increased with age. At 6 mo of age, 75% (9/12) of children who were sensitized to egg white had positive SPT to egg white. At 2 y, the proportion was only 14%. Similarly, only one of six children with IgE antibodies to birch was also SPT positive. Current smoking at home was admitted by 29% of the families and maternal smoking during pregnancy by 4%. Eighty-two percent of the children were breastfed for at least 1 mo, 44% for at least 3 mo and 15% for 6 mo or more.

Manifestations of allergic diseases ($p = 0.016$) and breastfeeding for less than 2 mo ($p = 0.005$) were the only risk factors that were significantly associated with sensitization, i.e. a positive SPT and/or circulating IgE antibodies to allergens at 2 y. Thus atopic heredity, parental smoking, gender, number of older siblings, pet ownership and factors related to the building conditions were not associated with either atopic symptoms or sensitization at 2 y.

Discussion

There are only a few prospective follow-up studies about allergic disorders in early childhood in industrialized countries. In some of the cohort studies the infants were non-selected, while the other cohorts included high-risk infants. Disease definitions, diagnosis, age of the children, evaluation of objective markers of atopy and testing procedures vary between countries and studies. It is therefore difficult to make comparisons. Some conclusions are reasonable, however; e.g. the 25% cumulative incidence of atopic diseases during the 2-y observation period in our study is similar to recent reports from Scandinavia and the UK on similar populations unselected with regard to a family history of allergy (12, 15, 16).

Atopic dermatitis was the main manifestation of atopy in all the studies and the cumulative incidence of 16% concurs with reports by Hattevig et al. (12, 17), Saarinen et al (18) and Arshad et al (19), but was higher than in 1974–75 in Sweden (20). This last-mentioned study was conducted more than 20 y ago and was based on a questionnaire, which may explain the low prevalence. A high rate of eczema was also reported in 1977 in New Zealand (21). Recent comparisons

between East and West Germany have shown a higher prevalence of AD among 5–7-y-old children in East Germany than in West Germany (22). Our study in young children supports the view that atopic dermatitis is not less common in Eastern than in Western Europe, despite the much lower prevalence of respiratory allergies in older children (1–5).

Four of 222 children developed asthma during the first 2 y of life. A similar incidence (1.7%) was reported by Hattevig et al. (12) in Swedish girls during a 4-y observation period. Much higher rates have been reported in other studies, e.g. 11% in the second year of life in the UK (16, 19) and 10% cumulative incidence over the first 18 mo in Denmark (23). The differences may be due to the diagnostic criteria. Respiratory illnesses with wheezing were as common in the Estonian infants as in other parts of the world (16, 19), but this was not accepted as asthma by our diagnostic criteria.

Stevenson et al. (24) have demonstrated that the underlying pathophysiologic mechanisms are different in virus-associated wheezing and asthma. For example, mast cells and eosinophils were elevated in bronchial alveolar lavage fluid from asthmatic children but not in children with virus-associated wheezing.

Only a few wheezing children in our study were sensitized to inhalant allergens or egg. The majority of infants with wheezing do not have an increased risk of asthma or allergies later in life and the condition is not mediated by IgE, but with small airways (25). However, in a minority of infants wheezing episodes may be related to a predisposition to asthma. The low prevalence of sensitization to inhalant allergens in Estonian schoolchildren (4) and in the present study in young children could support an inverse relationship between wheezing due to respiratory infections in early childhood and the later development of atopic manifestations.

Sensitivity to egg dominated among the 6 and 12-mo-old infants, while at 2 y cat and dog were the predominant allergens, which is similar to recent studies in Sweden (12, 13). Unexpectedly, circulating IgE antibodies to egg became more common with age, reaching 20% prevalence at 2 y. As expected from other studies (12), this was also true for circulating IgE antibodies to inhalant allergens. We can only speculate on the reasons for the low rate of positive SPT and the high rate of circulating IgE antibodies in the Estonian children. In an epidemiological study of Estonian schoolchildren we observed smaller mean histamine wheals than in similar studies in Sweden and a poor correlation between circulating IgE antibodies and the SPT results (4). Similar findings have been reported among Polish schoolchildren (3). The reasons for the poor correlation between SPT results and determination of circulating IgE antibodies in Estonia and Poland, as compared to Sweden, remain unexplained.

We and other investigators have recently reported

that the level of sensitization and allergic diseases is lower in the former socialist countries of Eastern and Central Europe (1–5). These studies were done in children over 6 y and in young adults. There are no previous studies in infants comparing the prevalence of atopic disorders and sensitization in Eastern and Western Europe. The similar prevalence of allergic manifestations during the first 2 y of life in this prospective study in Estonia and recent studies in Sweden could indicate that changes in lifestyle have already resulted in an increasing prevalence in Estonia.

An alternative explanation could be that IgE antibodies would be down-regulated with time in Estonian children (12, 13). The similar prevalence of positive SPT at 6, 12 and 24 mo in the Estonian children, while in Sweden the level of sensitization increased with age, could support the latter possibility. This down-regulation would be driven by environmental factors that have been lost to some extent in industrialized countries with a market economy, as suggested by epidemiological studies (5, 6) and animal experiments (9).

In conclusion, the similar prevalence of allergic symptoms and disease manifestations in young Estonian and Scandinavian children may be due to rapid changes in lifestyle, i.e. “westernization” in Estonia after regaining its independence in 1991. Alternatively, it could support the suggestion that there is a “temporal window of sensitization” (9) which will close more rapidly in Estonia than in Western Europe. A future follow-up of this cohort will provide more information regarding this possibility.

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