

# How do we define the high-risk groups for development of allergic disease?

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The high and increasing prevalence of atopic diseases such as bronchial asthma, atopic dermatitis, allergic rhinoconjunctivitis, urticaria and gastrointestinal allergy has led to attempts of prevention.

Identification of effective preventive strategies has to be exposed in high-risk groups before these measures are generally recommended (1).

As the first appearance of atopic disease is usually seen in the very young and sensitization is known to occur early, identification of high-risk groups has to be done as soon after birth as possible. Several methods have been used to identify those at particularly high risk of development of later atopic manifestations.

## **Genetic and environmental risk factors**

Many genetic and environmental factors are responsible for the phenotypic expression of atopic disease. A simple and reliable, i.e., both sensitive and specific, method for identification of high-risk groups is not present at this moment. Some prophylactic measures are simple, costless and well documented, and can be generally recommended without identification of high-risk groups.

Some of the genetic and environmental atopic risk factors are listed in Table 1. Studies concerning this topic are reviewed among others by Croner (2). None of these risk factors alone or in any combination, not even family history, has so far proved suitable for general allergy risk screening at birth.

Cord blood IgE concentration (CB-IgE) and the family history of atopic disease among parents and siblings are the variables most commonly used in predictive studies. In studies of unselected children at the ages of 18 months (3, 4), 7 years (5) and 11 years (6), it was concluded that increased CB-IgE levels were predictive of atopic disease. Another study of unselected children (7) concluded that fam-

ily history was more sensitive than CB-IgE in detecting infants at risk of atopy at 1 year of age.

Our follow-up study at the ages of 18 months (8, 9) and 5 years (10) could not confirm IgE as a predictor of atopic disease, but we found a statistically significant correlation between increased CB-IgE levels and subsequent development of allergy, i.e. atopic disease in combination with increased total IgE. CB-IgE was not predictive of non-IgE mediated disease. A similar conclusion was made in the German MAS-90 study (11). Several original papers and surveys reviewed in (10) concerning the predictive value of CB-IgE levels in children selected according to family history gave contradictory results. Many different CB-IgE cut-off values have been proposed. Our study indicated that a CB-IgE cut-off limit of 0.3 kU/l was the most reliable (9, 10).

Recently, specific IgE to foods (egg, cow's milk, peanut) determined by RAST or skin prick test in infancy exhibited high positive predictive values for food and aeroallergen sensitization (12).

In a prospective study CB-IgE, especially in combination with the family history, predicted sensitization and specific allergy defined as children with atopic disease combined with specific sensitization in RAST or in skin prick test (13).

Another recent study assessing several potential predictors of atopy concluded that family history in combination with CB-IgE, CB-eosinophils and dryness of skin in the neonatal period predicted atopic disease at 18 months of age (14). Predictive values for atopic disease in general including both IgE- and non-IgE-mediated disease in unselected subjects are listed for comparison in Table 2.

Especially the low and decreasing sensitivities during the follow-up period have led to the conclusion that CB-IgE is of limited use and not suitable for general allergy risk screening (15).

Table 1. Congenital and environmental risk factors for the development of atopic disease

|                                                        |  |
|--------------------------------------------------------|--|
| Congenital risk factors                                |  |
| Family history of atopic disease                       |  |
| Parental sensitization                                 |  |
| Male gender                                            |  |
| IgE in amniotic fluid                                  |  |
| Cord blood (CB) IgE                                    |  |
| IgE during the first week of life                      |  |
| IgE binding factors in CB                              |  |
| T-cell function in CB                                  |  |
| Eosinophils in CB                                      |  |
| Thrombocytes in CB                                     |  |
| Basophilic histamine release in CB                     |  |
| Linoleic acid in CB                                    |  |
| Cyclic adenosine monophosphate-phosphodiesterase in CB |  |
| Long-chain polyunsaturated fatty acids in breast milk  |  |
| Genetic markers on chromosomes 5, 7, 11                |  |
| Skin quality in neonates                               |  |
| Environmental risk factors                             |  |
| Exposure to drugs <i>in utero</i>                      |  |
| Exposure to tobacco smoke                              |  |
| Environmental pollution                                |  |
| Viral infections of the respiratory tract              |  |
| Early allergen exposure (foods, animals, mites)        |  |
| Breastfeeding practice                                 |  |
| Specific IgE, IgA and IgG antibodies to foods          |  |

In our study we evaluated CB-IgE as a possible predictor of IgE mediated disease and estimated predictive values in a high-risk group defined as children with a) biparental atopic predisposition or b) single severe atopic predisposition (one parent and/or one or more older siblings with perennial symptoms or symptoms from more than one organ system) and a CB-IgE value above a cut-off level of 0.3 kU/l. The predictive values were calculated for atopic disease, for allergy, defined as the combination of atopic disease and IgE high-response (total IgE > geometric mean + 1 SD among children without atopic disease), for bronchial asthma, for IgE-mediated bronchial asthma and for specific allergy, defined as children with atopic disease combined with specific sensitization in RAST or in skin prick test. The predictive values are listed in Table 3.

By combining the information on atopic predisposition and CB-IgE levels, it was possible to identify a small group of children with an increased risk of developing IgE-mediated disease especially asthma.

In a prospective study on the effect of a prophylactic program involving high-risk children, the cumulative prevalence of atopic disease up to 18 months of age was significantly lower in the prevention group compared to the control group (16). We still don't know whether a prophylactic program developed to postpone sensitization especially influences the development of IgE-mediated disease compared to non-IgE-mediated disease.

Table 2. Predictive values for atopic disease (IgE- and non-IgE-mediated) in unselected subjects

|                   |       |       |       |       |      |       |       |
|-------------------|-------|-------|-------|-------|------|-------|-------|
| Reference         | 3     | 5     | 6     | 4     | 7    | 8     | 10    |
| Year              | 1982  | 1984  | 1990  | 1988  | 1991 | 1992  | 1993  |
| Method            | PRIST | PRIST | PRIST | PACIA | EIA  | PRIST | PRIST |
| Follow-up (years) | 1.5   | 7     | 11    | 1.5   | 1    | 1.5   | 5     |
| Cut-off kU/l      | 1.3   | 0.9   | 0.9   | 1.2   | 0.6  | 0.5   | 0.3   |
| N                 | 1701  | 1651  | 1654  | 190   | 1023 | 1189  | 1189  |
| PPV (%)           | 70    | 58    | 67    | 72    | 24   | 43    | 42    |
| NPV (%)           | 95    | 88    | 72    | 92    | 78   | 62    | 64    |
| Sen (%)           | 44    | 40    | 26    | 68    | 9    | 17    | 34    |
| Spe (%)           | 98    | 94    | 94    | 93    | 92   | 86    | 71    |

According to the family history of atopic disease, it is necessary to be aware of the difficulties in obtaining a complete and true recording. As stated in (14, 17) it is necessary, but hardly obtainable to interview both parents to obtain a valid family history. Using a questionnaire alone may result in a major overestimation of atopic symptoms, especially in a normal clinical setting.

## Conclusion

Determination of CB-IgE in combination with a thoroughly obtained family history (biological parents) is still the most reliable way of selecting candidates for clinical trials of preventive measures. Skin prick tests or specific IgE in parental blood may improve the accuracy of the family history. In Denmark the government in 1993 wanted to reinforce strategies towards prevention of atopic disease. Official guidelines regarding primary prevention have been issued in 1994. Demarcation of a high-risk group is proposed with or without the use of CB-IgE and based on the family history as in this paper. Without using CB-IgE, the high-risk group consists of 16–20% of all newborns but tends to increase to 40–50%, if accuracy is not given concerning the rather rigid criteria regarding atopic predisposition. If, on the other hand, CB-IgE with a cut-off level of 0.3 kU/l is being used in combination with atopic disease, the high-risk group consists of 8–10%, minimizing the risk of stigmatisation. A standardized questionnaire filled in if possible by both parents before birth is preferable in any case. Some general advice concerning breastfeeding, introduction of

Table 3. Predictive values for atopic disease (A), allergy (B), bronchial asthma (C), allergic bronchial asthma (D) and specific allergy (E) in a high-risk group based upon family history and CB-IgE

|         |    |    |    |     |    |
|---------|----|----|----|-----|----|
|         | A  | B  | C  | D   | E  |
| PPV (%) | 59 | 26 | 27 | 20  | 30 |
| NPV (%) | 65 | 93 | 97 | 100 | 96 |
| Sen (%) | 17 | 33 | 50 | 87  | 48 |
| Spe (%) | 93 | 91 | 93 | 90  | 91 |

solid foods and environmental tobacco smoke exposure should not be limited to any high-risk group.

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