Changes in respiratory symptoms and airway hyperresponsiveness after 27 years in a population-based sample of school children


ABSTRACT: We wanted to test the hypothesis that childhood airway hyperresponsiveness, even in the absence of respiratory symptoms, is a risk factor for respiratory disease in adulthood.

In a childhood survey of 1963, three groups of 20 children aged 8–11 yrs, were selected from a population sample: 1) a group with recurrent respiratory symptoms (symptomatic group); 2) a group with no symptoms but a positive family history of atopy; and 3) a control group. All children completed assessment of symptoms, atopy, lung function, and airway hyperresponsiveness. At the adulthood survey 27 yrs later, 85% of the original sample were re-investigated.

Only 10 out of 19 subjects (53%) of the original symptomatic group still had symptoms. The significant difference of forced expiratory volume in one second (FEV1) % predicted in childhood between the symptomatic and the control group had disappeared. The prevalence of airway hyperresponsiveness had decreased in all groups. In asymptomatic hyperresponsive it had normalized at adult age. The asymptomatic hyperresponsive in childhood had lower levels of lung function, both in childhood and in adulthood. In univariate and multivariate analyses, respiratory symptoms at adult age were related to childhood atopy.

Results suggest that childhood atopy is a risk factor for respiratory symptoms in young adulthood, but that mild childhood airway hyperresponsiveness is not.

Eur Respir J., 1993, 6; 848-854.

Airway hyperresponsiveness (AH) is a major characteristic of asthma, the level of which correlates to the severity of symptoms in patients [1]. Although such a relationship of AH to symptoms is also present in epidemiological studies [2-4], the distribution of airway responsiveness appears to be continuous and unimodal, and a substantial overlap in values of responsiveness occurs between asthmatic and asymptomatic subjects [5-7].

Lile is known about the natural history of AH, especially in childhood. Although a genetic basis has been suggested [8, 9], AH appears to be highly variable in children [10, 11]. It can be induced or enhanced by lower respiratory tract infections in early childhood [12, 13], exposure to tobacoo smoke [14, 15], decreased aerial diameter [16], and, most strongly, by atopy [12, 17, 18]. Cross-sectional studies suggest that the prevalence of AH decreases with age until adulthood [18-20], along with a diminishing of asthma symptoms [21, 22]. In one longitudinal study in asthmatic children, a significant decrease in AH was seen 18 yrs later [23]. No follow-up data of similar duration of AH in epidemiological studies are yet available.

The relationship between AH in childhood and the development of respiratory symptoms and impaired lung function is unclear. Severe AH in childhood is a risk factor for ongoing respiratory symptoms [10, 23], and it is also related to impaired growth of the airways [24]. The clinical importance of AH among asymptomatic children is not known. Some studies have demonstrated that the presence of AH may precede the onset of respiratory symptoms [25, 26], suggesting that AH is a risk factor for the development of asthma. Another study showed that most asymptomatic children with mild AH are no longer hyperresponsive at follow-up [10].

We hypothesized that AH in childhood, even in the absence of respiratory symptoms, is a risk factor for recurrent respiratory symptoms at young adult age. This hypothesis was tested in a prospective study of school children, in which AH, respiratory symptoms and lung function parameters were reassessed after 27 yrs. A group of children with recurrent respiratory symptoms was compared to two groups of healthy symptom-free controls, with or without an atopic family history.

Methods

Study design

In 1963, a survey was performed among 477 children, 237 boys and 240 girls, aged 8–11 yrs, who were randomly selected from the population of the city of
Groningen, The Netherlands [27]. This random sample was formed in the following way: data from every inhabitant from Groningen in 1963 were present on small metal discs. The total length of this row of discs was 300 m. After a distance of 60 cm each time, every first child between 8-12 yrs of age was included in the study. Between October 1963 and February 1964, the parents of these children were visited at home by a single trained nurse. A standardized questionnaire [28] was used to determine present and past respiratory symptoms suggestive of asthma, and to record the family history of asthma and atopy. Of these children, 114 (24%) had recurrent respiratory symptoms (cough, phlegm, dyspnoea or wheeze).

Because constraints on time and finances in 1963 did not allow detailed assessment of the entire study population, a subsample of three groups of 20 children each, equally divided between both genders, was taken from the original group of 477: 1) 20 children with recurrent respiratory symptoms (symptomatic group); 2) 20 children without symptoms, but with a positive family history of atopy or asthma (family history group); 3) 20 children without symptoms or family history (control group). These 60 children, who were drawn from the original sample using random number tables, underwent tests of pulmonary function, airway responsiveness, and allergy.

Between March 1989 and March 1991, all subjects were invited to perform the same tests as in childhood. The original protocol of 1963 was applied in the same laboratory. Tests were performed in the months of January to May in both surveys. Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the University Hospital.

**Questionnaire**

The presence of respiratory symptoms was determined with a standardized questionnaire [28], extended with questions on the start and course of respiratory symptoms, smoking history, allergic symptoms [29], and use of medication. For the survey at adult age, respiratory symptoms were limited to the last 3 yrs. A positive family history of atopy was defined as the occurrence of asthma, hayfever, or atopic dermatitis among first degree relatives of a subject.

**Pulmonary function**

Pulmonary function measurements were carried out with a calibrated water sealed spirometer (Lode instruments, Groningen, The Netherlands). Inspiratory vital capacity (IVC) was measured, followed by forced expiratory volume in one second (FEV₁). The subjects repeated the tests until two technically satisfactory tracings, differing less than 5%, were produced. The highest value of these tracings was taken as baseline measurement for histamine challenge. Reference values for FEV₁, and IVC were calculated, using the prediction equations according to Zapel et al. [30] for the childhood survey, and according to the European Community for Coal and Steel [31] for the adulthood survey.

**Histamine challenge**

Airway responsiveness was assessed using a standardized histamine challenge test, as described in detail previously [32]. Following baseline measurements of pulmonary function, subjects inhaled nebulized distilled water from a Wiesbadener Doppel inhalation device. The airflow through the nebulizer was 4 l/min², resulting in an output of approximately 60 μl·min⁻¹. If the decrease in FEV₁, was less then 10% of baseline, the histamine challenge was continued. Sequential aerosols of histamine biphosphate, in concentrations of 0.25, 0.5, 1, 2, 4, 8, 16 and 32 mg·ml⁻¹, were inhaled for 30 s. After an interval of 1.5 min, IVC and FEV₁ measurements were made. The histamine concentration at which there was a decrease in FEV₁, of 20% or more of baseline was taken as the threshold value (PC₂₀). A PC₂₀ of 32 mg·ml⁻¹ using this protocol is equivalent to a PC₂₀ of 8 mg·ml⁻¹ using the conventional 2 min tidal breathing technique [32]. The test was discontinued if the threshold value was reached, or the highest concentration of histamine had been given. In the adulthood survey, a highest concentration of 64 mg·ml⁻¹ was used. AH was defined as any 20% decrease in FEV₁, following provocation. Subjects who did not reach the threshold value of FEV₁, were considered nonresponders. Histamine challenge was only performed if subjects had not used any asthma medication for at least 8 h.

**Eosinophils**

Blood eosinophils were counted in a Bürker counting chamber. The eosinophils were stained with eosin solution, containing 10 ml eosin 1%, 10 ml formol 40%, and water up to 100 ml.

**Skin tests**

All children were tested intradermally on the volar surface of the forearm, with 0.03 ml of the allergen solution (Diephuis Laboratory, The Netherlands). The following antigens were used: house-dust 0.5%, a mixture of animal dander 10%, a mixture of moulds 10%, and grass-pollen 1,000 Noon units·ml⁻¹. A coca solution served as a control. Fifteen minutes after application of the test, the greatest wheal diameter was measured. A test was considered positive, if the greatest wheal diameter exceeded 7.5 mm.

**Immunoglobulin E (IgE) measurement**

Because the exact composition of the childhood skin test allergens could not be reproduced, no reliable comparison between childhood and adult skin test reactivity was possible. Therefore, to determine atopic status in the survey at adult age, measurement of total serum IgE and antigen-specific IgE to house-dust mite, grasspollen, cat dander, and moulds was used. IgE measurements were performed using an enzyme immunoassay procedure.
Children from a study on childhood emigration (Pharmacia, Uppsala, Sweden). Results were expressed in kU·l⁻¹ (total IgE) or Phadebas radioallergosorbent test (RAST) units (PRU)·ml⁻¹ (specific IgE). Allergy was considered to be present if at least one of the antigen-specific IgE measurements was equal to or greater than 0.4 PRU·ml⁻¹.

Data analysis

Smoking history was expressed as pack-years, and as dichotomous variables indicating current and past smoking. Results of eosinophil counts and total IgE measurements were log-transformed to obtain a normal distribution. Data of the adulthood and the childhood study were analysed using paired or unpaired t-tests, or chi-squared tests, as appropriate. For independent assessment of the relationship between childhood factors and adulthood respiratory symptoms, a multiple logistic regression technique was used [33]. Results of the logistic regression analyses are presented as adjusted odds ratios (OR) and 95% confidence intervals (CI). All statistical procedures were performed with the SPSS-PC+ package. A p value <0.05 was considered statistically significant.

Results

At the second survey at adult age, 51 of the original 60 subjects (85%) co-operated in the entire protocol (symptomatic group 17, family history group 19, control group 15). An additional four subjects (2, 1 and 1, respectively) filled out the questionnaire forms, but were unwilling to undergo further testing. Three subjects refused to co-operate, while two could not be traced after emigration. Of these five missing subjects, only one had AH and none showed positive skin test reactivity in the childhood survey.

Childhood characteristics of the subjects who were investigated in both surveys are summarized in table 1. The three groups had comparable age distributions. Mean FEV₁, as a percentage of the predicted value (FEV₁, % pred) was significantly lower in the symptomatic group than in the control group. IVC expressed as percentage of the predicted value (IVC % pred) was not significantly different between groups. In the symptomatic group, AH was more common than in the asymptomatic groups. Skin test reactivity was less common in the control group than in the other two groups. Eosinophil counts in the three groups were not significantly different.

Results of the adulthood survey are presented in table 2. Smoking habits in the groups were comparable. Recent respiratory symptoms were significantly more common in the symptomatic and the family history group than in the control group. The prevalence of allergic symptoms was higher in the symptomatic group than in the control group. Atopy (presence of antigen-specific IgE), was more common in the symptomatic group than in the other two groups. There were no statistically significant differences between groups regarding FEV₁, % pred, IVC % pred, eosinophil count, total IgE, or prevalence of AH at adult age. We did not find a significant association between adulthood symptoms and past or current smoking.

A significant increase in FEV₁, % pred from the childhood to the adulthood survey was seen in the symptomatic group (p=0.02), and in the control group (p=0.03), but not in the family history group (p=0.57). The increase in IVC % pred reached significance in the control group (p<0.01), whilst a positive trend was seen in the symptomatic group (p=0.07).

Airway responsiveness

Figure 1 shows individual changes in PC₂₀ histamine from the childhood to the adulthood survey. Only three of the original 10 subjects from the symptomatic group who had AH in childhood still reacted to some extent to histamine at adult age. In this group, one nonresponder in childhood had mild AH in the adulthood survey.

<table>
<thead>
<tr>
<th>Table 1. – Childhood characteristics of the three study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
</tr>
<tr>
<td>Age mean (range) yrs</td>
</tr>
<tr>
<td>Male %</td>
</tr>
<tr>
<td>Recurrent respiratory symptoms n (%)</td>
</tr>
<tr>
<td>cough n (%)</td>
</tr>
<tr>
<td>phlegm n (%)</td>
</tr>
<tr>
<td>wheeze n (%)</td>
</tr>
<tr>
<td>dyspnoea n (%)</td>
</tr>
<tr>
<td>Family history* (%)</td>
</tr>
<tr>
<td>FEV₁ % pred mean (SD)</td>
</tr>
<tr>
<td>IVC % pred mean (SD)</td>
</tr>
<tr>
<td>Airway hyperresponsiveness** n %</td>
</tr>
<tr>
<td>Positive skin test n (%)</td>
</tr>
<tr>
<td>#log eosinophils mean (SD)</td>
</tr>
</tbody>
</table>

*: a positive family history of atopy was defined as the occurrence of asthma, hay fever or atopic dermatitis among first degree relatives; **: airway hyperresponsiveness was defined as any 20% decrease in FEV₁, following provocation, see text.; 1: p<0.05 compared to control group, Student's t-test for means. FEV₁: forced expiratory volume in one second; IVC: inspiratory vital capacity.
Table 2. - Adulthood characteristics of the three study groups

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Family history</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=19</td>
<td>n=20</td>
<td>n=16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age mean (range) yrs</th>
<th>36 (34-37)</th>
<th>36 (34-37)</th>
<th>36 (34-38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent respiratory symptoms in last 3 yrs n %</td>
<td>10 (53)</td>
<td>7 (35)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>cough n (%)</td>
<td>3 (16)</td>
<td>3 (15)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>phlegm n (%)</td>
<td>3 (16)</td>
<td>5 (25)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>wheeze n (%)</td>
<td>4 (21)</td>
<td>5 (25)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>dyspnoea n (%)</td>
<td>6 (32)</td>
<td>5 (25)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Allergic symptoms* n (%)</td>
<td>12 (63)</td>
<td>5 (25)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Family history* (%)</td>
<td>13 (68)</td>
<td>17 (85)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Current smoking n (%)</td>
<td>10 (53)</td>
<td>11 (55)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Pack-years mean (so)</td>
<td>8.4 (8.0)</td>
<td>7.9 (7.2)</td>
<td>7.7 (9.5)</td>
</tr>
<tr>
<td>FEV₁ % pred mean (so)</td>
<td>94.6 (14.1)</td>
<td>93.8 (15.8)</td>
<td>101.1 (12.2)</td>
</tr>
<tr>
<td>IVC % pred* mean (so)</td>
<td>94.7 (14.1)</td>
<td>96.3 (11.6)</td>
<td>102.2 (9.7)</td>
</tr>
<tr>
<td>Airway hyperresponsiveness* n %</td>
<td>4 (24)</td>
<td>3 (16)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Positive specific IgE* n (%)</td>
<td>9 (33)</td>
<td>7 (37)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>10 log total IgE mean (so)</td>
<td>2.0 (0.6)</td>
<td>1.8 (0.7)</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>10 log eosinophils mean (so)</td>
<td>1.8 (0.6)</td>
<td>1.9 (0.4)</td>
<td>1.8 (0.4)</td>
</tr>
</tbody>
</table>

* : see legend to table 1; ′ ′ : p<0.05 compared to control group, Student's t-test for means. IgE: immunoglobulin E. For further abbreviations see legend to table 1.

None of the eight childhood asymptomatic histamine-responders had a response on follow-up. Three subjects of the family history group and one of the control group had AH only at the adulthood survey.

All adults with a response to histamine in the symptomatic group reported respiratory symptoms during the last 3 yrs. In the family history group, 2 out of 3 hyper-responders had recent symptoms, whilst the histamine responder in the control group was asymptomatic.

**Relationship of childhood to adulthood characteristics**

The relationship of adulthood respiratory symptoms, airway obstruction, and AH to childhood characteristics was assessed both in univariate and multivariate analyses.

Respiratory symptoms at adult age were more common in subjects who showed skin test reactivity in childhood (64%) than in those who did not (28%, p=0.03). They were also more common in those who had wheezed as
a child (56%) than in those who had not (25%, p=0.03). There was no significant relationship of adulthood respiratory symptoms to gender, FEV1 % pred, hyperresponsiveness, smoking habits, or to the other respiratory symptoms in childhood.

In a logistic regression model, respiratory symptoms at adult age were related to childhood skin test reactivity, but not to the other childhood factors (table 3).

Table 3. - Adjusted odds ratio (OR) and 95% confidence intervals (CI) for adulthood respiratory symptoms by dichotomous childhood factors

<table>
<thead>
<tr>
<th>Childhood factor</th>
<th>Respiratory symptoms as an adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.5 0.6-10.3</td>
</tr>
<tr>
<td>Skin test reactivity</td>
<td>9.8 1.6-61.8</td>
</tr>
<tr>
<td>FEV1&lt;80% pred</td>
<td>1.5 0.2-9.4</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>3.1 0.8-12.5</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>1.0 0.2-4.2</td>
</tr>
<tr>
<td>Airway hyperresponsiveness*</td>
<td>0.7 0.1-3.2</td>
</tr>
</tbody>
</table>

*: PC<32 mg·mL⁻¹, see text. PC: provocative concentration of histamine producing a 20% fall in forced expiratory volume in one second (FEV1).

Adulthood FEV1 % pred was not significantly related to any of the childhood factors. Therefore, no multivariate analysis was performed.

Airway hyperresponsiveness (PC<32 mg·mL⁻¹) was more common in adults who were skin test reactors in childhood (36%) than in non-reactors (10%, p=0.03). Hyperresponsive subjects at adult age had a lower FEV1 % pred (mean (SD) 80.0 (15.5) %) than nonresponders (99.5 (11.5) %) (p<0.01). The asymptomatic hyperresponsive subjects in the childhood survey had a lower FEV1 % pred compared to asymptomatic nonresponders, both in childhood (84.6 (11.0) vs 94.9 (12.6) %, p=0.04), and at adult age (89.8 (8.7) vs 99.0 (15.6) %, p=0.05). No significant relationship was found between adulthood AH and gender, smoking habits, and childhood symptoms. Logistic regression analysis on adulthood AH was not considered feasible, because of the low prevalence of AH in the adulthood survey.

Discussion

In this longitudinal population-derived study, changes in respiratory symptoms and AH were assessed after an interval of 27 yrs. Because our study sample was small, results should be interpreted cautiously. Specifically, our study sample was too small to perform subgroup analyses of interest, such as the effect of severity of childhood symptoms, airway obstruction and AH on long-term outcome [10, 35]. Clearly, more population-based prospective studies are needed. A major problem of such investigations is the large loss to follow-up, which amounts to 40-60% in most reports [10, 11, 34, 35]. Although our study sample was small, our response rate of 85%, and our follow-up interval of 27 yrs, compare favourably to those of other studies.

In this study, which was performed in a group of children with recurrent respiratory symptoms and two groups of asymptomatic children, the prevalence of AH in the group of symptomatic children had diminished at adult age. All subjects in this group who were hyperresponsive to histamine in childhood had become nonresponders at adult age, or reacted only to the highest concentration of histamine. All children with AH in the asymptomatic groups showed no AH at adulthood. This reduction in severity and prevalence of AH has also been found in other prospective studies on AH in children. In a study among a hospital-derived population of asthmatic children, the prevalence of AH had decreased from 82 to 29% after a mean follow-up of 16 yrs [23]. In a large general population sample, a marked decrease in the number of children with mild to moderate AH, but not in the number of children with severe AH, was seen over 4 yrs of follow-up [10]. However, no decrease in the prevalence of AH was seen in a study among non-asthmatic, allergic children [34]. These findings corroborate cross-sectional studies [19, 20], showing an independent effect of age on AH. This decrease in AH is accompanied by a diminishing of respiratory symptoms and an increase in airway diameter, which is in accordance with earlier prospective studies [22, 35].

The results of our 27 yr follow-up study suggest that AH among asymptomatic children is a transient phenomenon. This finding, which is probably explained by the modulation of AH by exogenous factors [36], is in accordance with another study with much shorter follow-up [10]. The prognostic value of a single histamine provocation test in childhood for the development of chronic respiratory symptoms, therefore, appears to be small. When AH is repeatedly present in childhood, however, it does appear to be an independent risk factor for persisting respiratory symptoms [10]. Our results further show that asymptomatic AH in childhood is associated with a lower level of lung function at young adult age. This may be the result of reduced growth of airway calibre in hyperresponsive children [24]. Alternatively, the AH in asymptomatic children may reflect smaller airway diameter [16], which is usually persistent when children grow [37, 38].

The presence of atopy in childhood was related to respiratory symptoms and AH as an adult. The important role of childhood atopy as a risk factor for AH and the development of asthma has also been described in other, shorter prospective studies [35, 39]. Exposure to household allergens in early childhood appears to be an important determinant of the development of asthma [40], while long-term avoidance of allergens can reduce the level of airway responsiveness [41]. This suggests that early detection and treatment of atopy may prevent the development of recurrent respiratory symptoms, but the effectiveness of such early intervention remains to be determined.

Because of the large time-span between the first and the second survey, it was impossible to produce comparable skin test allergens. As differences in allergen composition and dilution are likely to influence skin test results, we chose to use measurements of specific serum
IgE for the most common aero-allergens to determine current atopic status. Although the difference in methodology makes comparison of results hazardous, the correlation between serum IgE concentrations and skin test reactivity in large epidemiological studies is high [42, 43]. Our results suggest that the prevalence of atopy has increased from childhood to adulthood in the group with respiratory symptoms in childhood (table 2). Other longitudinal studies show a peak in the prevalence of skin test reactivity [44], and serum IgE levels [42], between the ages of 25-35 yrs, coinciding with the age of our subjects during the second survey.

In our study, there was no significant difference between subjects with or without a family history of atopy with respect to respiratory symptoms at adult age. This is somewhat surprising because the hereditary basis of atopy is well-accepted [45]. One likely explanation for this result is the small sample size of our survey. Another factor might be the age of the subjects at the first survey. In children between 8-11 yrs possible atopic disease will already have manifested itself in most cases. In contrast to early-onset atopy, late-onset atopy is not consistently associated with asthma [35]. Thus, our study cannot answer the question of whether a positive family history of atopy is an independent risk factor for respiratory symptoms and impaired lung function at adult age. To address this issue, studies should start at an earlier age.

In conclusion, the prevalence of respiratory symptoms and AH decreases by about 50% after 27 yrs. The presence of AH in asymptomatic children, as determined by a single histamine challenge test, is not an important risk factor for the development of respiratory symptoms. In contrast, the presence of atopy in childhood is. This suggests that early detection and modulation of atopy is important, in order to prevent or reverse the development of recurrent respiratory symptoms.

References