Airway Hyperresponsiveness and Symptoms of Asthma in a Six-Year Follow-up Study of Childhood Asthma*

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**Background and aim:** In an inception cohort study of 457 asthmatic children diagnosed at the age of 3 to 4 years, airway hyperresponsiveness (AHR) was assessed 6 years after first diagnosis in a subgroup of 84 children. Our objective was to associate the level of AHR with the symptomatic asthma status at follow-up.

**Methods:** Information on respiratory symptoms and medication use for the previous 6 years was obtained. Children with reported wheezing episodes during the previous year (n = 169) or for ≥ 2 years at any time during the follow-up period (n = 85) were eligible for the challenge test.

**Results:** Among the 254 eligible children, 166 were randomly selected. The parents of 88 of them consented to have their child participate. At the time of assessment of AHR, 19 children (22%) were asymptomatic and 24 others (29%) had symptoms but did not use any medication. Forty-one children (49%) were symptomatic and required medication, including antiinflammatory preparations in 26 instances (31%). All but two children had significant AHR. There was no significant association between the level of AHR and graded symptomatic and medication score. Twenty-four of the 70 children (34%) with greatly enhanced AHR used no medication.

**Conclusions:** This study shows that (1) almost all children first diagnosed with asthma 6 years ago and with persisting but not necessarily current symptoms of asthma have increased AHR, which satisfies a proposed epidemiologic definition of asthma; (2) AHR was present in 95% of the 20 currently asymptomatic children; and (3) one third of children with greatly enhanced AHR did not use any treatment.

**Key words:** asthma; bronchial hyperresponsiveness

**Abbreviations:** AHR = airway hyperresponsiveness; BDT = bronchodilator; PC_{20} = concentration of methacholine causing a 20% fall in FEV_{1}

Several studies on the natural history of asthma have been conducted since 1960. In a cohort study of 454 children, including 371 aged 7 years and 83 aged 10 years at the time of entry, McNicol and Williams¹ found that approximately one third were still symptomatic at 21 years of age. This figure is comparable with the 27% figure found by Lebowitz and colleagues² in a cohort study of 568 children who were followed for 6 years after the initiation of the study. In these studies, information was obtained by questionnaire but was not confirmed by airway hyperresponsiveness (AHR). It has not been established whether persisting symptomatology during the follow-up period, with or without current symptoms at the time of assessment, is necessarily accompanied by AHR. The correspondence between recent or current asthmatic symptomatology and AHR is not perfect in most studies, as summarized by Woolcock and Peat.³ However, the combination of symptoms and AHR for defining asthma in epidemiologic studies presents advantages, because this discriminates individuals with disease from others inasmuch as neither one or the other appears sufficient in this regard.⁴

This study is part of a large inception cohort study to investigate the natural history of childhood asthma among 457 incident cases during a 6-year follow-up.
period. Our aim was to describe the level of AHR according to the asthma status at follow-up in a 20% subsample of children, reported to have presented with symptoms of asthma.

**Materials and Methods**

**Subjects**

A large inception cohort study was designed to investigate the natural history of childhood asthma among 457 asthmatic children in Montréal, Québec, Canada. These children had a first-time diagnosis of asthma (International Classification of Diseases, Ninth Revision, code 493) made by a pediatrician from 1988 to 1989 when they were 3 or 4 years old. The only criterion for eligibility besides no previous diagnosis of asthma was a residence in the greater Montréal area. The parents had been recruited at a hospital emergency room to participate in a case-control study designed to investigate the effects of indoor environmental factors on the incidence of asthma.5 From 1995 to 1996, the parents of 404 children (49 others were lost to follow-up and 4 refused) participated in a follow-up interview to determine the persistence of asthma 6 years after the first-time diagnosis. Of these, 254 were found eligible for assessment. Of these, 254 were found eligible for assessment. This was based on the persistence of symptoms. The rationale for this selection was to comply with the proposal of an epidemiologic definition of asthma based on two criteria: AHR and symptoms.4 Criteria for eligibility were as follows: (1) recurrent symptoms of asthma in the last year of follow-up or (2) no symptom of asthma in the preceding year but recurrent symptoms during ≥2 years during the follow-up period, as obtained by a positive answer to at least one of the following questions: (1) “Has your child had an attack of wheezing that has caused him or her to be short of breath after the first diagnosis?” (2) “Does your child’s chest occasionally sound wheezy or whistling when she or he is not suffering from a cold?” (3) “Has your child ever been taken to the emergency for an attack of asthma?” and (4) “Does your child use or has your child used medication for the treatment of asthma?” Of the 166 randomly selected subjects who satisfied the eligibility criteria, we decided to assess airway responsiveness in approximately 20% of children in the cohort. The parents of 78 of 166 refused to participate, leaving 88 children (53%) who underwent assessment of AHR.

**Data Collection**

An information letter was sent to the parents of the 457 children included in the initial case-control study. Trained interviewers conducted a telephone interview with the parents using a questionnaire derived partly from the children’s questionnaire from the Epidemiology Standardization Project.6 The questionnaire documented (1) the respiratory symptomatology, with standard questions on frequency of cough, wheezing, and attacks of wheezing; (2) the treatment for asthma, with detailed questions on type of medication and frequency of use; and (3) emergency room visits and other factors, related mostly to the child’s environment, which are not presented here. Five categories of symptomatic and medication status were therefore set: (1) no symptoms, no medication; (2) no symptoms, medication; (3) symptoms, no medication; (4) symptoms, bronchodilators (BDT); and (5) symptoms, anti-inflammatory medication.

The data on health history were obtained separately for each year during the follow-up period. The information from the most recent years was used to classify the children into five categories (see Results).

**Table 1** shows the results from the comparison of demographic and clinical features between participants in the bronchial challenge test, other eligible but not tested children, and the refusals. Participants, other eligible but not tested children, and those who refused were comparable with respect to sex distribution, clinical features, use of anti-inflammatory medication at follow-up, and the presence of clinical symptoms of asthma in the preceding year. These variables had the same distribution in participants and nonparticipants owing to refusal, except for clinical features at follow-up: no children were reported as being asymptomatic and using medication among nonparticipants, and a greater proportion of children were symptomatic and untreated in that group than among participants.

**Results**

Figure 1 shows individual results of PC_{20} according to baseline FEV_{1} and symptomatic status. Airway responsiveness could not be estimated in four children; two had a baseline FEV_{1} < 70% predicted, one was unable to perform the test, and the other had a hyperventilation reaction. FEV_{1} values (mean ± SD) in the five categories of symptomatic status were as follows: no symptoms, no medication, 89.6 ± 15.4% predicted; no symptoms, medication, 94.6 ± 7.8% predicted; symptoms, no medication, 88.6 ± 12.2% predicted; symptoms, BDT, 85.6 ± 9.9% predicted; and symptoms, anti-inflammatory medication, 92.7 ± 11.0% predicted. An FEV_{1} < 80% predicted was documented in 21.6% of an epidemiologic definition of asthma based on two criteria: the rationale for this selection was to comply with the proposal of an epidemiologic definition of asthma based on two criteria: AHR and symptoms.4 Criteria for eligibility were as follows: (1) recurrent symptoms of asthma in the last year of follow-up or (2) no symptom of asthma in the preceding year but recurrent symptoms during ≥2 years during the follow-up period, as obtained by a positive answer to at least one of the following questions: (1) “Has your child had an attack of wheezing that has caused him or her to be short of breath after the first diagnosis?” (2) “Does your child’s chest occasionally sound wheezy or whistling when she or he is not suffering from a cold?” (3) “Has your child ever been taken to the emergency for an attack of asthma?” and (4) “Does your child use or has your child used medication for the treatment of asthma?” Of the 166 randomly selected subjects who satisfied the eligibility criteria, we decided to assess airway responsiveness in approximately 20% of children in the cohort. The parents of 78 of 166 refused to participate, leaving 88 children (53%) who underwent assessment of AHR.

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of subjects, including 28.6% of asymptomatic untreated children; in 29.2% of symptomatic untreated children; in 20% of symptomatic children treated with BDT; in 15.4% of symptomatic children on anti-inflammatory medication; and in none of the asymptomatic treated children. As shown in Figure 1, all but two PC20 values were in the AHR range.

Table 2 shows the distribution of subjects according to PC20 and asthma status at follow-up based on symptoms and medication need during the preceding 2 years. During the preceding year, 29 children had been treated with inhaled corticosteroids. The frequency of use was known for 26 of them. Only 2 had received regular inhaled corticosteroid therapy whereas the others were on short-term courses. The majority of children (all but two) with symptoms of wheezing or with medication requirement, even for a short interval during the 6-year follow-up period, had significant AHR (PC20 < 8 mg/mL).

Among the 82 children with AHR at follow-up, 78% had current symptoms suggestive of asthma. When grouping the children with the two highest scores, 35 of 40 children (87.5%) had a PC20 < 2 mg/mL, whereas a similar proportion of 83.3% was found among children in the other three categories reflecting mild or no asthma. As many as 18 of 24 children (75%) reporting to be symptomatic but not currently receiving any medication for their asthma had a PC20 < 2 mg/mL.

Table 3 shows the association between airway responsiveness and symptoms reported by parents. Half of this sample of children who were ever symptomatic in the follow-up period had experienced at least one attack of wheezing during the preceding 2 years, with a slightly lower proportion for wheezing occasionally apart from colds, and <20% for chronic cough. The proportion of children with reported attacks of wheezing or current wheezing in the previous 2 years increased with the level of AHR.

**Discussion**

This study shows that virtually all children with a physician-made diagnosis of asthma at the time of a visit to an emergency room and who reported symptoms at any time during the 6-year follow-up period demonstrated AHR. These children therefore satisfy a recently proposed epidemiologic definition of asthma as evidenced by symptoms and AHR. Toelle and coworkers showed that these two criteria clearly delineate individuals with features that are different.

![Figure 1. Bronchial responsiveness as expressed in log PC20 by FEV1 (percent predicted) and status of asthma at follow-up. There was a significant relationship between log PC20 and percent predicted FEV1 (r = 0.38, p < 0.01).](image-url)
from those with one or the other but not both; these individuals have enhanced severity of both clinical and functional measures when compared with those who have one or the other feature. Moreover, in a follow-up study of 236 children aged 8 to 11 years seen 1 year later, all children studied by this group of investigators continued to demonstrate AHR, and 93% still had symptoms of wheezing. This was interpreted as further evidence of persisting asthma.10 Kolnaar and colleagues11 also showed, in a cross-sectional survey of 551 adolescents and young adults, that symptomatic subjects with AHR had highly different atopic and clinical characteristics from asymptomatic subjects without AHR; in addition, the latter did not differ in this respect from asymptomatic subjects with AHR. Symptoms and AHR are thus key features to be considered.

Our study group of 84 children assessed for AHR was generally representative of the 254 children who were currently symptomatic or had ever been symptomatic during the 6-year period except that they had fewer symptoms.

Other studies that were cross-sectional surveys examined symptoms and AHR in children, adolescents, and young adults.12–15 They observed that the sensitivity of AHR in documenting asthma, based on current symptoms reported in questionnaires, can be variable, ranging from 45 to 100% using a cut-point of PC20 \(\leq 8\) mg/mL, and around 20 to 36% at PC20 \(\leq 2\) mg/mL; however, its specificity, particularly if a threshold of PC20 \(\leq 2\) mg/mL is selected,12,15 is consistently very high (on the order of 90%).13,14 In this sample of 84 children from the inception cohort of asthmatic children who were symptomatic at one time or another during the previous 6 years, the proportion with PC20 \(\leq 8\) mg/mL was 98% (n = 83) and 83% (n = 70) for a cut-point of \(< 2\) mg/mL. A similar proportion was found (ie, 82% at a PC20 \(\leq 2\) mg/mL) if only children currently symptomatic were considered (53 of 65 children). This, however, contrasts with the findings by Kolnaar and colleagues,16 who, in a cross-sectional population-based study of 551 subjects aged 10 to 23 years, reported that only 50% of those with a PC20 \(< 2\) mg/mL reported symptoms compatible with asthma.

The reason why the majority of our symptomatic children had greatly enhanced AHR (PC20 \(\leq 2\) mg/mL) could well be that studying children who were first diagnosed as asthmatic in the emergency room

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>PC20 (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–0.125</td>
</tr>
<tr>
<td>No symptoms, no medication</td>
<td>1</td>
</tr>
<tr>
<td>No symptoms, BDT</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms, no medication</td>
<td>1</td>
</tr>
<tr>
<td>Symptoms, BDT</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms, anti-inflammatory medication</td>
<td>3</td>
</tr>
<tr>
<td>All (%)</td>
<td>10 (12)</td>
</tr>
</tbody>
</table>

*A PC20 value > 8 mg/mL corresponds to normal responsiveness.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>PC20 (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one attack of wheezing</td>
<td></td>
</tr>
<tr>
<td>During the 6-yr interval, No. (%)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>During the preceding 2 yr, No. (%)</td>
<td>(n = 60)</td>
</tr>
<tr>
<td>Wheezing†</td>
<td></td>
</tr>
<tr>
<td>During the 6-yr interval, No. (%)</td>
<td>(n = 80)</td>
</tr>
<tr>
<td>During the preceding 2 yr, No. (%)</td>
<td>(n = 60)</td>
</tr>
<tr>
<td>Chronic cough</td>
<td></td>
</tr>
<tr>
<td>During the 6-yr interval, No. (%)</td>
<td>(n = 30)</td>
</tr>
<tr>
<td>During the preceding 2 yr, No. (%)</td>
<td>(n = 2)</td>
</tr>
</tbody>
</table>

*Data are given as No. (%).
†A PC20 value > 8 mg/mL corresponds to normal responsiveness.
‡Wheezing occasionally, apart from colds.
resulted in the selection of a group with a firmer diagnosis than children paying office visits to a pediatrician.

A significant proportion (19 of 84 children, 23%) included in this group did not have symptoms at the time of assessment. This includes 17 subjects with PC\textsubscript{20} < 2 mg/mL, which otherwise would make them very likely to be symptomatic. Several explanations for this can be proposed. First, parents may deny the current symptomatic status because of the social and psychological impact of admitting having a child with asthma. Many parents are also informed that children with asthma often outgrow their asthma, modifying their perception of symptoms and biasing their answers to the questionnaire. Second, perception of symptoms is low in some individuals, which can be a risk factor for developing severe asthma because of delay in administering adequate therapy.\textsuperscript{17} Third, the questionnaire was administered to parents and not to children. Children might have been more aware of their symptomatic status. However, Fitzgerald and colleagues\textsuperscript{15} recently showed that there was a high agreement between asthma questionnaires administered to parents and children.

Fourth, asymptomatic AHR is a well-recognized situation as recently reviewed by Jansen et al\textsuperscript{18}; the evolution of asymptomatic AHR has been described in prospective studies, where it was found that 14%\textsuperscript{19}, 35\%,\textsuperscript{20} 40\%,\textsuperscript{21} and 58\%\textsuperscript{22} of subjects with AHR developed asthmatic symptoms at a later stage. In all these studies, the fact that the assessment of AHR made subjects more aware of past, current, or subsequent symptomatology was not excluded. Indeed, causing a significant fall in FEV\textsubscript{1} during methacholine testing and asking subjects whether this causes symptoms that mimic current symptomatology has been proposed as a useful guide to a clinical diagnosis of asthma, more helpful than respiratory questionnaires.\textsuperscript{23} None of these studies were initiated at the time of the initial diagnosis of asthma, which is the interest of our cohort and clearly differentiates our group from subjects included in other prospective studies.

It is still somewhat surprising to realize that only 26 of 65 symptomatic children (40\%), including 53 with PC\textsubscript{20} < 2 mg/mL, were on anti-inflammatory preparation. Clearly, many of these children would have required such treatment as recommended in several published guidelines\textsuperscript{24} and widely available at the time of this follow-up. It is known that asthma remains undertreated for many reasons, including cost and fear of side effects in the case of inhaled steroids, especially in children.\textsuperscript{25,26} Therefore, we feel that the prognosis would have been much better if treatment had been optimally prescribed, includ-
nonspecific bronchial responsiveness in a pediatric population. Chest 1991; 100:927–934
17 Barnes PJ. Poorly perceived asthma. Thorax 1992; 47:408–409
18 Jansen DF, Timens W, Draan J, et al. (A)symptomatic bronchial hyper-responsiveness and asthma. Respir Med 1997; 91:121–134
26 Lipworth BJ, Segal JR. Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids. Thorax 1997; 52:476–482