Asthma and asthma-like disorder, a 5-year follow-up study

O. Löwhagen, M. Arvidsson, and K. Pettersson

Asthma and Allergy Research Group, Department of Respiratory Medicine and Allergy, Sahlgrenska University Hospital, Göteborg, Sweden.

Abstract Consecutive adult patients (n = 70) referred for investigation of suspected asthma were reinvestigated after 5 years with the same diagnostic procedures (airway symptom score, spirometry, methacholine test) as used at the initial investigation. The same diagnostic criteria for asthma, asthma-like disorder (current asthma-like symptoms but negative asthma tests) and chronic obstructive pulmonary disease (COPD) were used at both visits. At the first visit 39/70 patients (56%) fulfilled the asthma criteria, 21/70 (27%) fulfilled the asthma-like criteria and 5/70 (7%) the COPD criteria. Due to lack of current symptoms 5/70 (7%) could not be classified. 5/70 patients (7%) were smokers, however, in the majority (72%) smoking was not tolerated as it induced asthma-like symptoms. At the first visit, 5 years later, 30/39 patients (76%) still fulfilled the asthma criteria and 12/21 patients (57%) still fulfilled the asthma-like criteria. At the 5-year investigation, 10% of patients in the asthma group now fulfilled the asthma-like criteria and 10% of patients in the asthma-like group fulfilled the asthma criteria. It is concluded that asthma as well as an asthma-like syndrome may persist for 5 years or more. It is also concluded that the two disorders are closely related as patients in the asthma group over time could move into the diagnostic criteria of the asthma-like disorder and vice versa.

INTRODUCTION

Asthma is defined as a disorder with bronchial inflammation, reversible bronchial obstruction and bronchial hyperreactivity. The diagnostic criteria have been established in international consensus reports (1–4). In an asthma and allergy clinic, it has frequently been observed that some patients present asthma-like symptoms (breathlessness, difficulty in getting air, cough, etc.) but, despite severe symptoms, have no reversibility to a β2-agonist or bronchial hyperreactivity as measured by a methacholine test. The question has been raised whether these patients have a latent or a mild asthma, that may progress into a manifest asthma or whether this disorder is another type of asthma, as asthma-like symptoms associated with subjective hyperreactivity (5–11) and sensory hyperreactivity have been described (12,13).

The aim of this study was to systematically investigate consecutively included patients with lower airway problems and after 5 years to reinvestigate these patients with the same diagnostic criteria and procedures in order to analyse changes in diagnoses and values of diagnostic parameters used (symptoms, bronchial obstruction, reversibility, hyperreactivity).

PATIENTS AND METHODS

The study included 70 patients, 53 women and 17 men. The mean age was 41 years, with a range of 17–67 years. All patients were referred to our outpatient clinic for investigation of suspected asthma and were consecutively included in the study. None of the patients had visited an asthma specialist before. The duration of the airway symptoms varied between 1 and 48 years, with a mean of 9 years. Before admission, 62 patients (89%) had been prescribed β2-stimulants by inhalation and of these, 12 (19%) reported no effect. Inhaled steroids had been prescribed in 34 patients (49%). Exact efficacy could not be assessed, as the drug compliance was low. The investigation involved physical examination, questionnaire for assessment of airway symptoms and symptoms induced by trigger factors, FEV1 with β2-reversibility, diurnal variation in PEF (peak expiratory flow rate) with β2-reversibil-
ity, and methacholine test. Five years later all investigations were repeated in exactly the same way.

**Questionnaire**

The questionnaire included 26 common respiratory/chest symptoms, such as wheezing, heavy breathing, tightness, cough, secretion, etc. Each patient graded the frequency of symptoms on a scale from 0 to 3 (0 = never, 1 = sometimes, 2 = often, 3 = daily symptoms). Questions had the following formula: ‘How often do you experience wheezing?’ The severity of symptoms from 12 common trigger factors — cold air, exercise, tobacco smoke, perfumes, exhaust gases, chemicals, flower scents, etc. — were also scored 0–3 (0 = no, 1 = mild, 2 = moderate and 3 = severe symptoms). These questions followed this formula: ‘What degree of breathing problems do you experience when you are running?’ ‘What degree of breathing trouble do you experience from perfumes?’ In order to be classified as ‘positive’ (current symptoms) a symptom score ≥ 2 was required.

**Airway function tests**

FEV₁ was measured before and after 0.8 mg inhaled salbutamol. Two reproducible forced expiration curves were required each time. Short- and long-acting bronchodilators were not allowed within 4 and 12 h before the test, respectively. Peak expiratory flow rate (PEF) was measured morning and night before and after 0.8 mg inhaled salbutamol over a period of 14 days. The best value of two was noted on a special protocol. The patients were instructed not to take other short- or long-acting bronchodilators during this period. Mean morning and mean night values were expressed as percentage of predicted value. The reversibility was expressed as the percentage change of the pre-β₂-agonist value. Variability during the period was expressed as the percentage difference between the lowest PEF (morning before the β₂-agonist) and the highest value (evening after the β₂-agonist) (3).

**Methacholine test**

A methacholine test was performed according to a standardised method (14,15). Neither short- nor long-acting bronchodilators were allowed within 4 and 12 h, respectively, before the test. The patient inhaled NaCl (starting volume 2 ml) for 2 min, with the FEV₁ value after NaCl as the baseline. This value should be at least 65% of the expected value. Two-fold increasing doses were given by doubling the concentration of methacholine starting with 0.03 mg/ml. The interval between doses was 5 min. FEV₁ was recorded 2 and 4 min after the end of each dose. The test was terminated when the fall in FEV₁ was more than 20%, or when the maximum dose (16 mg/ml) was reached. The threshold dose which gave a fall in FEV₁ ≥ 20% (a value slightly higher than corresponding PC20-value) was used. The limit for a positive response was a threshold dose < 4 mg/ml.

**Skin-prick test (SPT)**

STP was performed with 12 common inhalant allergens: house dust mite, mould, cat, dog, horse and pollen (birch, grass and mugwort). The weals were graded traditionally in a plus system in relation to the weal of histamine which was set to 3+.

**Medication**

After the investigation medication was changed and adapted to the current severity of the disease. For an approximate comparison of medication (β₂-agonists and inhaled steroids) between the two visits a stepwise grading (0–4) was used according the following: 0) no asthma medication; 1) bronchodilators as required; 2) addition of inhaled steroids up to 1000 μg/day; 3) addition of inhaled steroids > 1000 μg/day; and 4) addition of oral steroids. The inhaled steroids used (beclomethasone and budesonide) were considered equipotent. Long-acting β₂-agonists and leucotriene inhibitors could not be compared, as they were not generally used at the time of the initial investigation. For practical and ethical reasons a complete control of compliance and prescribed medication made by different physicians could not be conducted during the observation period.

**Diagnostic criteria**

For the diagnosis of asthma the following two criteria should be fulfilled: (1) airway symptoms (wheezing, breathing trouble, cough or phlegm) graded ≥ 2 in the questionnaire; and (2) at least one of the following: ≥ 10% increase of mean morning PEF, ≥ 10% increase in FEV₁ after 0.8 mg inhaled salbutamol, or a threshold dose of methacholine < 4 mg/ml. For an asthma-like disorder the following criteria should be fulfilled: (1) Airway symptoms (wheezing, breathing trouble, cough or phlegm) graded ≥ 2; (2) < 10% increase of mean morning PEF or < 10% increase in FEV₁ after 0.8 mg inhaled salbutamol or a threshold dose of methacholine ≥ 4 mg/ml; and (3) mean morning PEF or FEV₁ ≥ 80% predicted (for excluding a non-reversible bronchial obstruction such as COPD).

**Statistical methods**

Standard methods were used for calculation of mean, SD and correlation coefficient (r). Differences between
groups were analysed with non-parametric tests. For statistical significance a $P$-value of $< 0.05$ was required.

RESULTS

Drop out

In the initial study (year 0) all patients carried out the investigations. At year 5, six patients failed to attend the clinical investigation, three were not willing to participate and three had moved far away. Three patients in year 0 and eight patients in year 5 were not willing to have a methacholine test.

Diagnoses year 0

Of the 70 patients 39 (56%) fulfilled the criteria for asthma and 21 (27%) fulfilled the criteria for asthma-like disorder. Five patients (7%) had a PEF or FEV$_1$ < 80% predicted and reversibility < 10% (COPD-like group). All five were non-smokers. An additional five patients (7%) could not be classified due to lack of data or symptoms (symptom score < 2). Seventy-two percent of all patients reported airway symptoms to smoke (symptom score ≥ 2).

Diagnoses year 5

Of 70 patients, 35 (50%) fulfilled the criteria for asthma and 19 (29%) fulfilled criteria for asthma-like disorder. Of the remaining patients two (3%) had a non-reversible bronchial obstruction (COPD-like group) and 14 (20%) could not be classified. Seven did not attend and seven did not report enough symptoms.

Changes in diagnoses from year 0 to year 5

At the 5-year investigation, 30/39 patients (76%) in the asthma group from year 0 still fulfilled the asthma criteria. Four patients (10%) had moved into the criteria of an asthma-like disorder, two (8%) had moved into the COPD-like group, and three (8%) could not be classified. After 5 years, 12/21 patients (57%) in the asthma-like group still fulfilled the same criteria, 2/21 (10%) now fulfilled the asthma criteria, and 7/21 (33%) could not be classified (no symptoms or no attendance). Of the five COPD-like patients at year 0, two now fulfilled the asthma criteria and two the asthma-like criteria. In total, at the 5-year investigation, 35/70 patients (50%) fulfilled the asthma criteria, 19/70 (27%) fulfilled the asthma-like criteria, 2/70 (3%) were COPD-like, and 14/70 could not be classified due to lack of data ($n = 9$) or not enough symptoms ($n = 5$).

Skin-prick test

Of the 39/70 patients who fulfilled asthma criteria, 13 (33%) had a positive SPT. Of the 21/70 patients who fulfilled the criteria for an asthma-like disorder, 9 (43%) had a positive skin-prick test.

Medication

After the initial investigation, 29/39 patients (74%) in the asthma group, and 4/21 patients (19%) in the asthma-like group were prescribed (in addition to a bronchodilator) inhaled steroids in a dose ≤ 1000 μg/day. None was prescribed a higher dose or an oral steroid on a daily basis. After the 5-year investigation, 25/39 patients in the asthma group (64%), and 6/21 patients (29%) in the asthma-like group were prescribed inhaled steroids. Five out of 39 patients (13%) in the asthma group but none in the asthma-like group were prescribed a dose > 1000 μg/day. None was prescribed an oral steroid on a regular basis. Ten out of 39 patients in the asthma group, and 9/21 in the asthma-like group only had an inhaled β$_2$-agonist when needed.

DISCUSSION

In this study, we believe that three important observations have been made. The first is that patients with asthma or asthma-like symptoms of similar severity may have asthma or an asthma-like disorder, which may not be classified as COPD or a healthy stage. The second observation is that this disorder may persist for 5 years or more. The third is that asthma and the asthma-like disorder may be closely related, as asthma in some patients moved over time into the diagnostic criteria of the asthma-like disorder and vice versa. As asthma and asthma-like disorders appear to be so closely related, the most important conclusion is that asthma-like disorders must be considered in future asthma studies. In both diseases there are asthma-like symptoms, but the asthma-like disorders must be separated by the absence of bronchial obstruction and bronchial hyperresponsiveness. However, separation of two disorders may be difficult in some cases as the two disorders (or mechanisms) may be present in the same patient. The observation that the asthma-like disorder persisted for at least 5 years does not support the hypothesis that this disorder is a pre-stage to asthma. It could also be the other way around, as some patients in the asthma group moved into the criteria for an asthma-like disorder. The number of patients in this initial observational study is limited, and a study with a larger number of patients during even longer period of time may therefore be important.

Although in each study patient was referred for the investigation of suspected asthma, the participants are not representative of all types of patients with asthma.
and asthma-like symptoms. However, they were consecutively included in the investigation and may represent patients with more severe disease and patients in whom the diagnosis of asthma has been problematic. The diagnostic criteria chosen are in accordance with recent guidelines (1–4) where it is stressed that diagnosis of asthma should be based on the presence of episodic airway symptoms and reversible airflow obstruction and the exclusion of alternative diagnoses. However, the exact values for a 'positive' result are crucial and are not given for all diagnostic parameters in the consensus reports, with two exceptions, reversibility to a $\beta_2$-agonist $\geq 12\%$ (3) and PEF-variability $> 20\%$ (3). Different diagnostic criteria with different values for a positive result have been used in various studies and, as in this study, they may be discussed. However, even if the diagnostic procedures and the values for a positive result in this study had been chosen in a slightly different way the main result of the two key groups would have been the same.

As in all clinical follow-up studies the influence of medication on the diagnostic methods may be considered, especially of steroids, as they may reduce bronchial hyperresponsiveness and improve lung function. For ethical reasons, treatment must always be given and a complete control during a long period of time is not easy to perform. Most patients in the asthma group were prescribed inhaled steroids compared to only a few in the asthma-like group. An improvement in the mean values of lung function, reversibility and hyperresponsiveness was also seen in the asthma group (Table 1), and it may be speculated that patients in this group may have moved into the criteria of an asthma-like disorder due to positive effects of treatment. However, only 10% of the asthma group moved that way and the majority still fulfilled the asthma criteria after 5 years. The possibility of normalising or improving lung function and hyperresponsiveness by asthma treatment underlines the need for a careful registration of airway symptoms and trigger factors as there are yet few other diagnostic parameters available (23).

Asthma-like symptoms not directly related to bronchial obstruction have been discussed only sparingly in recent consensus reports (1–4). In other literature there is an increasing use of the term 'asthma-like' which may indicate a growing awareness of the existence of asthma-like symptoms not directly related to reversible airway obstruction. However, there seems to be no previous study in adults where the diagnoses of asthma and asthma-like disorders have been critically compared and reinvestigated after a certain period of time. In a recent consensus some differential diagnoses in adults, such as COPD, laryngeal dysfunction, cough secondary to drugs, and vocal cord dysfunction are listed (3), but none of these seems to be similar to the asthma-like disorder found in this study. COPD due to smoking is often reported as a common differential diagnosis. Nevertheless, in this study, carried out in an asthma and allergy clinic, signs of a non-reversible bronchial obstruction were found in only a few patients, all of whom were non-smokers. In patients with asthma-like cough and secretion chronic bronchitis is a differential diagnosis. However, chronic bronchitis, when not due to smoking, may be a non-specific disorder. In this study only five patients (7%) were smokers and in the majority of the patients (72%) smoke was not tolerated as it induced asthma-like symptoms. For studying mechanisms and aetiology in these cases, we think it is more fruitful to focus on type of airway symptoms, trigger factors and bronchial hyperreactivity.

Other disorders with asthma-like symptoms have been described, including the hyperventilation syndrome (16–18), 'ski asthma' (19,20) and multiple chemical sensitivity (21,22). It is possible that some of our patients could have these disorders, but the study was not designed to answer such questions. It is also likely that some of our patients may have a sensory hyperreactivity (12,15), as

<table>
<thead>
<tr>
<th>Year 0 (mean, range)</th>
<th>All</th>
<th>Asthma</th>
<th>Asthma-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0 (mean, range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 % pred.</td>
<td>98</td>
<td>91</td>
<td>110</td>
</tr>
<tr>
<td>FEV1 % revers.</td>
<td>8</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>PEF % pred.</td>
<td>82</td>
<td>76</td>
<td>95</td>
</tr>
<tr>
<td>PEF% revers.</td>
<td>13</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Methacholine (median)</td>
<td>2.0</td>
<td>0.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Year 5 (mean, range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 % pred.</td>
<td>93</td>
<td>88</td>
<td>106</td>
</tr>
<tr>
<td>FEV1 % revers.</td>
<td>6</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>PEF % pred.</td>
<td>90</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>PEF% revers.</td>
<td>10</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Methacholine (median)</td>
<td>4.0</td>
<td>1.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>
cough and breathing troubles induced by odours were reported among many of them. Capsaicin, a stimulant of sensory nerves, is used to verify a sensory hyperreactivity (12), but the test was not in use at the start of this study.

As pointed out above, even if the inclusion criteria had been selected or combined in a different way the main results for the two patient groups would have been the same. For example, if a positive reversibility in FEV₁ was set to ≥12%, only one of the patients in the asthma group would be classified as non-asthma (moving into the asthma-like group). If a PEF variability ≥20% had been included in the diagnostic criteria for asthma, only one asthma patient would have been classified as non-asthma (moving into the asthma-like group). As bronchial obstruction and β-reversibility are key points in the clinical diagnostics of asthma (1–4), we consistently measured PEF during a 2-week period before and after a β₂-agonist. A mean morning reversibility of 10% was chosen as the limit for a positive result since good correlation with the FEV₁-reversibility had been found in earlier pilot studies. If the methacholine test had been excluded as a diagnostic test, the subdivision of the two main groups would have been similar. The methacholine test may be positive for disorders other than asthma but a negative test may strongly exclude asthma (3,6,8,15). For this reason, the test may be valuable when separating asthma from an asthma-like disorder. In consensus reports the presence of symptoms has been stressed (2–4). All patients in the present study had current episodic airway symptoms at the initial investigation, but after 5 years, five patients no longer had symptoms according to the initial criteria. The severity of symptoms in the two groups was not exactly compared as only the lower limit for symptom score was determined. Measuring symptoms is not an easy task as there are many different airway symptoms, such as wheezing, cough, secretion, breathing troubles, chest tightness, symptoms at night, symptoms induced by different trigger factors, etc. Which are most specific for asthma? Extensive studies of airway symptoms that may be associated with asthma and asthma-like disorders, respectively, are now in progress (23).

From the observations made in this follow-up study we conclude that some patients with asthma-like symptoms may not have asthma, COPD or a healthy state. Our first hypothesis is that there are one or more asthma-like disorders, such as sensory hyperreactivity, that must be seriously considered in future clinical studies of asthma. Our second hypothesis is that these disorders may be common and may clinically, although not fatal, be as severe as 'classical' asthma.

REFERENCES

9. Ringsberg KC. Patients with asthma-like symptoms but with negative asthma tests and patients with bronchial asthma. Physiological, psychological and social characteristics. Medical Dissertation, No. 522, Linköpings University, Sweden, 1997.