Outcome and severity of adult onset asthma—Report from the obstructive lung disease in northern Sweden studies (OLIN)

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Predictors

Summary
Background: Studies of longitudinal changes in severity and the long-term outcome of asthma in epidemiological settings are uncommon.
Aim: To assess the outcome of incident asthma in a cohort of subjects who developed asthma after the age of 20 years.
Methods: This is a prospective study of the outcome of 309 subjects with incident asthma being included in a case-referent study based on all adults aged 20–60 years living in three municipalities/towns in Northern Sweden. The subjects fulfilled the criteria for incident asthma defined as onset of symptoms common in asthma within 12 months prior to the study and a verified bronchial variability. In 2003, 250 (81%) of the subjects with asthma were re-examined with structured interview, lung-function test and methacholine test.
Results: At follow-up, 237 (95%) subjects still had an active asthma, i.e. they had symptoms or used asthma medicines. Among those with active asthma, 65% were using inhaled cortico-steroids. Severity grading (GINA 2000) showed that 21% had mild intermittent asthma, 30% mild persistent, 44% moderate persistent, and 5% severe asthma, contrasting to 75% with moderate or severe asthma at entry. Higher age, higher BMI and low lung function were associated with greater asthma severity. Twelve subjects (5%) were in remission. Predictors for remission were non-sensitisation and a normal lung function. Age, sex, BMI, and smoking habits were not significantly different between those in remission and those not.
Conclusions: Remission of adult onset asthma was low. Severity of asthma changed considerably over time, however, the overall change was towards a milder disease probably as a result of treatment.

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Introduction

Longitudinal studies of the long-term outcome of asthma and changes in severity over time are few. In particular follow-ups of subjects with an adult onset of asthma are uncommon. Asthma is defined as a chronic disease. However, remission of asthma may occur, and is more common in children than in adults. The proportion remitting asthma in a population is dependent upon the age composition of the samples and the length of follow-up, as relapses of asthma are common among teenagers and young adults post a remission period. Furthermore, different definitions of remission affect the observed remission rates.

Most studies about the outcome of asthma are based on cohorts of children or young adults, i.e. studies of asthma patients diagnosed at young age. Clinical remission of childhood asthma, i.e. no symptoms and no use of asthma medicines, has been reported to be around 50%. Using these criteria for remission, a 10-year follow-up of a population study based cohort of adult asthmatics resulted in a remission of 6%. Predictors of remission are not well known, however, a low level of lung function in childhood, a high degree of bronchial hyper-reactivity, and being allergic are reported to be negative factors for remission. On the contrary, some studies have not found any association between atopy and remission of asthma.

Although the severity of asthma varies over time and may be related to long-term outcome, factors related to degree of severity are not well known and understood. Some studies have reported that severe asthma among adults is more common among non-allergic subjects, particularly among the middle-aged. However, change of severity over time and factors related to change in severity are poorly studied in population-based studies of asthma.

Within the Obstructive Lung Disease in Northern Sweden Studies (OLIN) several cohorts are under study. One of them is a well-characterised cohort of subjects with adult onset asthma, which has been followed-up. The aim of this study was to identify factors related to the severity of asthma in the cohort, change in severity, remission rate of asthma, and predictors of remission.

Materials and methods

Study population

The asthma cohort consisted of cases with incident adult asthma recruited from 1995 to 1999 in Northern Sweden. Briefly, the cohort consisted at inception of 309 subjects aged 20–60 years at time of inclusion. The inclusion criteria were a history of asthma with onset of symptoms common in asthma within the last 12 months prior to the inclusion and a physiologically verified bronchial variability either by a methacholine test, a reversibility test, or peak expiratory flow (PEF) variability. The cohort and the inclusion criteria at baseline have been reported in detail elsewhere. Thus, the examination at inclusion included a structured interview, lung-function test, methacholine test, and further a skin prick test (SPT). A reversibility test or measures of morning and evening PEF was performed in subjects with contra-indication for methacholine testing. The methacholine test was not performed in subjects with FEV1 < 65% of predicted, in subjects with ischemic or other cardiovascular disease, or in pregnant women. Subjects with previous childhood asthma was excluded from the study.

The follow-up visits were performed in 2003, and the mean follow-up time was 70 months (SD 17). At the follow-up visit, 250 asthmatics participated at a structured interview, 237 satisfactorily completed a lung-function test, and 187 a methacholine test. The same methods were used at the follow-up visits as at the study inclusion. The ethical committee at the University of Umeå approved the studies.

Structured interview

The interview questionnaire included questions from the OLIN questionnaire, the International Union Against Tuberculosis and Lung Diseases (IUATLD) questionnaire, and the interview questionnaire developed for the European Community Respiratory Health Survey (ECRHS). Thus, questions about a family history of asthma and allergy, rhinitis, hay fever, eczema, smoking habits and occupation were included.

Skin prick test (SPT)

The tests were performed with allergen in 50% glycerol using a lancet with a tip of 1 mm. The allergens were cat, dog, horse, birch, timothy, mugwort, Dermatophagoides farinae, D. pteronyssinus, Cladosporium and Alternaria (Soluprick, ALK, Denmark). A positive reaction was recorded if the diameter of the wheal was ≥ 3 mm after 15 min.

Lung-function test and methacholine test

The lung-function tests were performed following the American Thoracic Society (ATS) recommendations using a dry spirometer, Mijnhardt Vicatest 5. Swedish reference values were used. Methacholine tests were performed with an Aiolos nebulizer and an electricity-driven compressor. The method was calibrated against the method described by Hargreave and Juniper.
Definitions

Remission of asthma: Four different criteria for remission were defined. First, subjects were defined as having remitted from their asthma if they did not report any wheeze or attacks of shortness of breath during the last 12 months, and had not used any asthma medicines during the last 12 months. Further definitions included also normal lung function and no hyper-reactivity defined as PC20 at two different cutoffs of the concentration of methacholine chloride, ≥4 mg/ml and ≥8 mg/ml, respectively.

Family history of asthma: Asthma among father, mother or a sibling.

Smoking habits: Smoking habits were classified based on the reported smoking habits both at baseline and at follow-up. Subjects were defined as smokers if they smoked every week or had stopped smoking within the preceding 12 months. Those who had stopped smoking ≥12 months prior to the first study were classified as ex-smokers. Five smoking categories were created: non-smokers, ex-smokers, smokers, quitters, and starters or re-starters.

Rhinitis: Subjects reported that they often had nasal blocking or a running nose.

Eczema: Subjects reporting past or present eczema.

Body mass index (BMI): Weight in kilograms divided by the square of the height in meters (kg/m²).

Positive skin test: A weal ≥3 mm to any of the tested allergens.

Asthma severity: Grading the severity of asthma followed the GINA classification from year 2000 based on day and night symptoms, lung function, and medication.22 As the GINA-classification was developed later than the initial study design, the frequency of night symptoms was not surveyed at the inclusion visit of the study. Further, it was not possible to retrospectively separate moderate and severe day symptoms, why moderate and severe day symptoms are grouped together in the inclusion data.

Statistical methods

Statistical analyses were performed using SPSS version 11.0. Comparisons of proportions were tested with chi-square test or Fishers’ exact test. Continuous data is expressed in mean ± SD, and comparisons of means were tested with two-tailed Student’s t-test. One way analysis of variance (ANOVA) was used for test for trends. A p-Value of <0.05 was regarded as statistically significant. Covariates used in the analyses that may influence both severity and remission of asthma included age, sex, smoking habits, BMI, allergic sensitisation, concomitant rhinitis, and level of FEV1 in percent of predicted. Multiple logistic regression models were performed using these independent variables as risk factors (odd ratios, OR, with 95% confidence intervals, CI) of asthma severity. The dependent variable “asthma severity” was dichotomised first by combining the moderate and severe asthma groups versus the combination of the two milder groups, and secondly by comparing the severe asthma group versus the three other severity groups. The study lacked power to test predictors of remission by using multivariate analyses.

Results

Of the 309 asthmatics included in the original cohort, the majority were still living in the area and were invited to the follow-ups, and 250 subjects participated corresponding to 81% of the cohort. The participation rate was lowest, 58%, among subjects aged 20–29 years, while it was 88–93% in all other 10-year age groups. The participation rate was lower among men (Table 1).

Remission

Twelve subjects, 4.8%, fulfilled the first criteria for remission, i.e. did not report any wheeze or attacks of shortness of breath and had not used any asthma medicines during the last 12 months. When the criterion of the remission were strengthened, and also absence of bronchial hyper-reactivity was included in the criteria, the remission rate decreased further (Fig. 1). The observation time was similar in the subjects who had remitted their asthma and those who had not.

Subjects in remission had a statistically higher mean FEV1% predicted at the study inclusion compared with subjects who did not remit their asthma. No major difference in PC20 at study inclusion was found between those in remission and those not. None of the 12 subjects in remission had been a smoker during the study period, while 23% of those with continuing asthma had been a smoker at either enrolment, follow-up, or at any time during the study period, p = 0.074. Absence of rhinitis and a negative SPT were more common among remitters. Age, sex, or BMI did not differ significantly between those in remission and those not (Table 2). Ever having had eczema or a family history of asthma did not influence remission. Neither did use of ICS at

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Among subjects with incident asthma; number of invited, participants, and subjects in remission at follow-up, by age and sex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of asthma</td>
<td>Sex</td>
</tr>
<tr>
<td>20–29 y</td>
<td>30–39 y</td>
</tr>
<tr>
<td>Invited, n</td>
<td>89</td>
</tr>
<tr>
<td>Participated, n (%)</td>
<td>52 (58)</td>
</tr>
<tr>
<td>Remissiona, n (%)</td>
<td>3</td>
</tr>
</tbody>
</table>

aRemission defined as no symptoms and no use of asthma medication during the last 12 months.
any time during the study period: 92% among those in remission versus 88% among those still having asthma.

Symptoms and medication in non-remitters

Among the 238 subjects still having asthma at follow-up, 78% reported wheeze during the last 12 months, 91% attacks of shortness of breath, and 28% reported night symptoms. Sixty-five percent of the subjects were using inhaled corticosteroids (ICS) as mono-therapy or in combination with long-acting beta-2-agonists (LABA), and 25% were using fixed combination of ICS and LABA at follow-up. Further, 49% used or had used medication for rhinitis or rhinoconjunctivitis.

Severity grading

Grading of severity of asthma using the year 2000 GINA-classification at follow-up showed that 21% had mild intermittent asthma, 30% mild persistent, 44% moderate persistent, and 5% severe asthma. At study inclusion, the corresponding figures had been 9%, 16%, while 75% had either moderate persistent or severe asthma. At enrolment, the "severity class driver" was symptoms, while at follow-up use of medicines was the most important driver of severity class (Table 3). The change of severity class from baseline to follow-up did not follow any specific pattern, and the severity grade varied considerably from enrolment to follow-up (Fig. 2).

At follow-up, severity of asthma (GINA 2000) according to bi-variate analysis was not significantly related to allergic sensitisation, although 25% of those with severe asthma had a positive skin prick test compared to 39% of those with mild intermittent and 46% with mild persistent asthma. Low FEV₁ and increasing age were related to increased asthma severity (Table 4). Subjects with severe asthma at follow-up had significantly increased their BMI during the study period (Table 4). No significant difference in smoking habits between the severity groups was found, however, nine of the 12 subjects with severe asthma had never been smokers. Rhinitis had no influence on the severity of asthma (Table 4).

According to multivariate analyses, only low FEV₁ at the follow-up visit was significantly related to severe asthma: OR 0.92 (95% CI 0.87–0.97) for a decrease in percent of predicted with 1% unit. When moderate and severe asthma were combined, the combination was significantly associated with low FEV₁ (OR 0.95, 95% CI 0.93–0.97) and increasing age. Compared with the age group <35 years, age 35–54 years yielded an OR of 3.1 (1.2–7.9) and age 35–44 years OR 2.7 (1.1–6.8) for moderate and severe asthma. No other significant associations were found using the multivariate analyses.

Discussion

To the best of our knowledge, this is the first study investigating the longitudinal outcome of an adult asthma cohort only including subjects with adult onset asthma with the strict exclusion of subjects who had asthma during ARTICLE IN PRESS

Table 2 Basic characteristics in subjects in remission and in subjects still having asthma at the follow up visit.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Still having asthma (n = 238)</th>
<th>Remission (n = 12)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at follow-up, mean year (SD)</td>
<td>44.2 (10.4)</td>
<td>40.5 (6.5)</td>
<td>0.219</td>
</tr>
<tr>
<td>Sex, women, (%)</td>
<td>69</td>
<td>83</td>
<td>0.356</td>
</tr>
<tr>
<td>BMI at follow-up, mean (SD)</td>
<td>26.8 (4.6)</td>
<td>26.4 (6.1)</td>
<td>0.758</td>
</tr>
<tr>
<td>BMI change from baseline, mean (SD)</td>
<td>+0.9 (2.1)</td>
<td>+1.1 (2.2)</td>
<td>0.771</td>
</tr>
<tr>
<td>FEV₁% predicted at baseline, mean (SD)</td>
<td>92.6 (13.7)</td>
<td>101.3 (12.5)</td>
<td>0.033</td>
</tr>
<tr>
<td>FEV₁% predicted at follow-up, mean (SD)</td>
<td>95.2 (15.1)</td>
<td>101.6 (13.2)</td>
<td>0.214</td>
</tr>
<tr>
<td>Positive skin prick test at baseline, (%)</td>
<td>41.8</td>
<td>9.1</td>
<td>0.051</td>
</tr>
<tr>
<td>Rhinitis at baseline, (%)</td>
<td>57.6</td>
<td>25.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Rhinitis at follow-up, (%)</td>
<td>47.5</td>
<td>8.3</td>
<td>0.007</td>
</tr>
<tr>
<td>Smoking any time during study period, (%)</td>
<td>23.1</td>
<td>0</td>
<td>0.074</td>
</tr>
<tr>
<td>Smoking categories during the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>n = 108</td>
<td>n = 7</td>
<td></td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>n = 75</td>
<td>n = 5</td>
<td></td>
</tr>
<tr>
<td>Quitters</td>
<td>n = 19</td>
<td>n = 0</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>n = 29</td>
<td>n = 0</td>
<td></td>
</tr>
<tr>
<td>Starters and re-starters</td>
<td>n = 7</td>
<td>n = 0</td>
<td></td>
</tr>
</tbody>
</table>
childhood. All subjects had their first onset of asthma symptoms between the ages of 20 to 59 years, and their asthma and symptoms common in asthma as well had lasted less than 12 months at the beginning of the observation period. The study confirms that adult onset asthma is a chronic disease with a low remission rate. The rate of clinical remission was 0.8/100/year. The remission rate was even lower, 0.5/100/year, when absence of bronchial hyper-reactivity and normal lung function were added to the criteria defining remission.

The validity of the results must be judged as high due to a number of reasons. The participation both at enrolment and follow-up was high, and the loss of follow-up was low. The diagnosis of asthma had a high specificity as both a history of asthma and a physiological verification of the diagnosis was required, while sensitivity was not optimal. The enrolled asthmatics had all contacted health care for their symptoms before the examinations that preceded inclusion. Subjects with mild intermittent asthma may not have been included and remission may have been somewhat underestimated. Nevertheless, all enrolled asthmatics had a clinically relevant disease, which demanded them to seek health care. Inter-observer bias could be avoided as the same team examined the patients both at enrolment and at follow-up.

Previous studies focusing on remission have been based on asthmatics identified in cross-sectional studies or in clinical settings, and the duration of asthma before the start of follow-up in these studies has varied considerably. A well-defined Dutch cohort of asthmatics was followed-up after 25 years. The asthmatics were 13–44 years old at entry, and in total were 181 subjects followed-up. When remission was defined as no symptoms, 40% were in remission and the average remission rate was 1.6/100/year. Further, 20% were not hyper-reactive, while only about 10% had a normal lung function, no hyper-reactivity, and were free from symptoms corresponding to an annual remission rate of 0.4/100/year, a result similar to ours. In Northern Sweden, an asthma cohort derived from a general population sample was identified by using clinically defined criteria of asthma based on medical history and physiologically verified bronchial variability. At 10-year follow-up, the mean annual remission rate was 0.6/100/year. Remission in that study was defined as no symptoms and no use of asthma medicines during the last 12 months. Remission of asthma as well as reports about remission in the Tucson study and some other US studies were limited to questionnaire reports without physical examination or lung function testing. Thus the reported remission rates were based on reports by the patients and no other information than absence of symptoms was available.

When the age composition is even younger at study entry, remission rates are seen to increase. A recently published 12 year follow-up of a Danish sample aged 7–17 years at entry yielded a remission of 40%. In a 30-year follow-up of a Dutch childhood-asthma cohort, 52% were in clinical remission, although 57% of those in clinical remission still were hyper-reactive. The greater proportion of those who were hyper-reactive can in part be explained by results from

<table>
<thead>
<tr>
<th>Severity</th>
<th>Day symptoms Baseline</th>
<th>Follow-up</th>
<th>Night symptoms Baseline</th>
<th>Follow-up</th>
<th>Lung function Baseline</th>
<th>Follow-up</th>
<th>Asthma medication Baseline</th>
<th>Follow-up</th>
<th>Over all scoring Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
<td>13.4</td>
<td>56.3</td>
<td>a</td>
<td>94.1</td>
<td>86.3</td>
<td>20.6</td>
<td>40.3</td>
<td>73.5</td>
<td>44.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>15.5</td>
<td>23.9</td>
<td>b</td>
<td>71.0</td>
<td>19.3</td>
<td>1.7</td>
<td>10.9</td>
<td>44.1</td>
<td>31.1</td>
<td>0</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>15.5</td>
<td>34.4</td>
<td>a</td>
<td>71.0</td>
<td>19.3</td>
<td>1.7</td>
<td>10.9</td>
<td>44.1</td>
<td>31.1</td>
<td>0</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>a</td>
<td>0.4</td>
<td>a</td>
<td>0.4</td>
<td>b</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

Percentages by severity (%) of all participants.
a not able to classify. b moderate or severe symptom class.
another Dutch study showing eosinophils, T-cells, mast cells and interleukin-5 in the mucosa of asthmatics in clinical remission. The somewhat greater proportion in remission without hyper-reactivity in our study compared with the Dutch studies may be a result of a rather short follow-up period of five to six years since the onset of asthma and thus
a short time for remodelling to occur. As smoking was inversely related to remission, the relatively low proportion of smokers in our study may have contributed to the slightly higher remission rate compared with the first referred Dutch study and our previous study based on prevalent cases of asthma.

As found in the Dutch and the Tucson study, predictors of remission in our study were mild disease and normal lung function at onset of asthma. Active smoking decreased the possibility of remission, as did rhinitis and allergic sensitisation. Interestingly, factors for development of asthma in the same cohort was studied by a case-referent model and risk factors for incident asthma in adulthood were a family history of asthma, rhinitis, increased BMI, ex-smoking, and allergic sensitisation.

An important result was the observation that severity of asthma changed considerably over time. The GINA guidelines from year 2000 suggest four severity grades of asthma. When using the GINA-classification of severity, three out of four of the asthmatics had moderate or severe asthma at enrolment mainly due to frequent symptoms, but less than a half were classified as moderate or severe at follow-up. At enrolment only 9% had mild intermittent asthma versus 21% at follow-up. The large proportion classified as moderate or severe according to GINA at entry may at least in part be a result related to the new onset of disease. At onset, the large majority reported frequent symptoms. Thus most cases of incident asthma did not start as a mild intermittent or mild persistent asthma. The incident asthma subjects would not have been adapted to their airway symptoms, which may explain the frequent reporting of symptoms.

Our result of changed severity is not supported by results from the ECRHS, which found severity at baseline to be an important determinant of severity at follow-up. This result of the ECRHS may be explained by the fact that the asthmatics in the ECRHS were identified by a cross-sectional survey in contrast to the asthmatics in our study. The change of severity observed in our study may reflect the nature and course of asthma in patients introduced to asthma medication. A further contributing factor to the observed decline in overall severity could be the recent onset of asthma, which may have been accompanied by varying pathophysiological processes and remodelling of airways parallel to treatment with ICS in two-thirds of the cohort, delaying processes that decrease reversibility including remodelling of the airways. The main reason in the large proportional decrease in severity is probably an effect of treatment, mainly maintenance treatment with ICS.

In these asthmatic subjects with an adult onset, somewhat less than a half were sensitised to common airborne allergens when diagnosed. Additionally, the risk factor pattern was similar both in the atopic and the non-atopic asthmatics, results conforming to data from the ECRHS.

Remission was however, inversely associated with allergic sensitisation, results in accordance with some studies, but in contrast with other. Our study shows that in adults, atopy is a risk factor for the chronicity of asthma. The lower proportion of sensitised severe asthmatics in our study conforms to the results from the European study of severe adult asthma, Enfumosa, which showed that the majority of severe asthmatics had a reduced risk of being sensitised to common aero-allergens. The results conform also to a Danish study, in which prognosis with regard to lung function was poorer in subjects with non-atopic compared with atopic asthma.

Multivariate analyses indicated that low lung function at entry was associated with increased severity. Also increasing age was significantly associated with severity, and the association was confirmed by the multivariate analyses. Increased BMI did not reach statistical significance as a risk for moderate or severe asthma in the multivariate setting. However, in subjects with severe asthma at follow-up, BMI had increased with 2.9 units (mean), which reflects an average weight increase of about 9 kg, results in accordance with a French study showing overweight to be related to uncontrolled asthma. Thus, weight reduction could be an important strategy for improvement in asthma among obese subjects. However, the risk factor pattern for severe asthma is still poorly understood.

In conclusion, the annual remission rate of newly identified cases of adult onset asthma followed over five years was less than 1%. Remission was related to mild disease, normal lung function at onset, absence of allergic sensitisation, rhinitis, and being a non-smoker. Atopy was a predictor of sustained asthma, and increase in BMI was related to severe asthma at follow-up. Increasing age and low lung function were predictors of severe asthma. Severity of asthma according to the GINA-classification varied considerably though the relatively short follow-up period and tended to decrease probably as a result of treatment.

Conflict of interest statement

Louise Watson was employed by GlaxoSmithKline for the years 2002–2005, who have been partial sponsors of the study. None of the other authors have any conflict of interest to declare in relation to this work.

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