Predictors of the persistence of childhood asthma

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ABSTRACT

Background. The factors relevant to the prognosis of childhood asthma differ from one population to another.

Objectives. To characterize the course of childhood asthma in the catchment area of our hospital, and to identify prognostic factors for this population.

Methods. All children given a diagnosis of asthma in the paediatric pulmonology service of a tertiary hospital were followed up for 5 years.

Results. Satisfactory control of asthma was achieved in 69 % of cases. The factors identified as associated with poor control were allergy to cats and pollen, a large number of crises in the year prior to diagnosis, and younger age at onset.

Conclusions. In our region, childhood asthma has a relatively favourable prognosis. The subsequent course of the disease appears to be determined in childhood. The persistence of symptoms appears to depend to a significant extent on the degree of atopy.

Key words: Allergy. Longitudinal study. Paediatric asthma. Prognostic factor.

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INTRODUCTION

Recent decades have seen increases in the prevalence of childhood asthma, which, depending on the country considered, ranged from 2.1 % to 32.2 %[1]. Although asthma involves both genetic and environmental factors, these increases appear most probably to have been due to the latter[1].

Asthma being a chronic condition of variable course, it would seem desirable to identify factors associated with persistent disease so as to be able to identify asthmatic children with the greatest risk of persistence. Preferential attention to these patients would hopefully improve their long-term prognosis.

The factors that in previous studies have been found to increase the risk of persistence include other atopies, exposure to tobacco smoke, bronchial hyperresponsiveness, impaired lung function, and the severity of the disease[1]. In this work we studied the course of childhood asthma in the catchment area of our centre (the area around Santiago de Compostela, Spain; with a population of around 387,000 people covered by the public health system), and factors that might determine unfavourable prognosis.

MATERIALS AND METHODS

Patients and study design

The 669 children (60 % boys) who between June 1991 and February 1993 were given a diagnosis of asthma in the Allergy and Pulmonology Unit of the Paediatrics Department of the University Hospital, Santiago de Compostela (Spain), were each followed up for 5 years. *A posteriori,* we included in this study

the 249 (161 boys and 88 girls) whose records lacked no more than two of the data required for the study (see below, Study variables) and who, throughout follow-up, had been free of the following other conditions: a chronic pulmonary disease other than asthma, neuromuscular disease, mental retardation, gastro-oesophageal reflux, and chronic sinusitis.

Diagnosis and management

Diagnosis was carried out by the two paediatric respiratory physicians of the Unit (the same two throughout the study) in accordance with the guidelines of the U.S. National Asthma Education Program Expert Panel Report of 1991 (USNAEPEPR)[2]. Briefly, asthma was diagnosed if *a*) bronchodilatory treatment resolved recurrent episodes of coughing, dyspnea, wheezing or intolerance of exercise for which other aetiologies had been ruled out, and *b*) for children aged 6 years or more, with compatible clinical symptoms and with spirometric results including a positive bronchodilation test consistent with a diagnosis of asthma. The severity of the disease was evaluated following U.S. National Institutes of Health (NIH) guidelines[3].

All patients were provided with printed instructions on how to react to changes in symptoms, and with a list of nine recommendations for control of their environment. All were re-examined at least once a year in the same Unit.

During the course of the study the patients were managed by the physicians responsible for their diagnoses in accordance with USNAEPEPR 1991 guidelines[2]: mild asthma was treated with beta-2 agonists *ad lib*, and more severe forms already based on inhaled corticosteroids. Peak expiratory flow (PEF) was evaluated at each visit, and forced spirometry was performed at least once a year. Treatment was prescribed at each visit on the basis of severity and in view of the degree of adherence to treatment and environmental control recommendations. These patients can receive medicines for free.

Study variables and evaluation methods

The following parameters were studied, where pertinent, at each examination: sex; month of birth; age at diagnosis; age at onset of asthma; age of first consultation prompted by symptoms of asthma; family history of allergy (considering parents, siblings, parents' siblings and grandparents); the child's history of allergy; parents' smoking behaviour; presence of dogs or cats at home; number of crises or hospitalization episodes in the year prior to diagnosis, eosinophils in peripheral blood; serum IgE; skin test results for mites, grass pollen, dog, cat, *Alternaria alternata* and *Aspergillus fumigatus* (allergen extracts commercially available, from ALK-Abello); the severity of asthma, spirometric parameters (including bronchodilatory test results), treatment received, adherence to treatment, number of crises or hospitalization episodes during follow-up, and degree of control at 5-year follow-up.

Skin tests were performed as per Kurlat[4]. Adherence to therapy was evaluated on the basis of self-report plus observation of inhaler technique; adherence was deemed good if inhaler technique was correct and seven of the nine environmental control recommendations had been complied with. Asthma was deemed to be controlled if the patient had no symptoms, reported no limitation of everyday activity (including exercise), had normal PEF with a circadian variability of less than 20 %, and only very occasionally had to resort to beta-2 agonists[3].

Statistical analysis

Statistical distributions were tested for deviation from normality using Kolmogorov-Smirnov tests. Normally distributed variables were compared using Student's *t* tests or analyses of variance, and non-normally distributed variables using Kruskal-Wallis or Mann-Whitney *U* tests. Variables shown by univariate analyses to be associated with differences in degree of control of asthma were subjected to multivariate logistic regression analysis for identification of the variables with independent effects and calculation of the corresponding odds ratios. All statistical analyses were performed using SPSS v.6.0.

RESULTS

At diagnosis, the 249 patients included in the study were aged 7.08 ± 3.09 years (range 4-14 years). Some 49 % lived in rural localities and 51 % in urban localities.

Only 12 patients (5 %) had persistent severe asthma at diagnosis, and for the purposes of statistical analysis they were pooled with the patients with persistent moderate asthma. This joint condition was more common among boys than among girls at diagnosis (Table I), and was diagnosed at a later age than less severe forms (Table II).

Asthma was associated with allergy in 227 cases (91 %), and in all these cases there was allergy to

Table I

Distribution of the sample, by sex and severity of asthma

	Boys *n* (%)	Girls *n* (%)	*p**
Intermittent	46 (29 %)	27 (31 %)	< 0.05
Mild	34 (21 %)	32 (36 %)	
Moderate and severe	81 (50 %)	29 (33 %)	
Total	161 (100 %)	88 (100 %)	

*For comparison of percentage of boys with percentage of girls.

Table II

Mean age at onset of symptoms and mean age at diagnosis, for each severity. Data are means ± standard deviations

	Age at onset of symptoms (years)	*p*	Age at diagnosis (years)	*p*
Intermittent	3.25 ± 2.57	Ns	6.18 ± 2.51	< 0.01
Mild	3.50 ± 2.52		7.30 ± 3.22	
Moderate and severe	2.76 ± 2.68		7.55 ± 3.41	

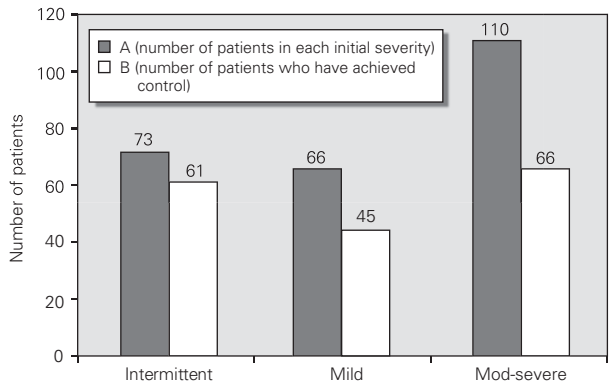

Figure 1.—Numbers of patients in each initial severity class who had achieved control of asthma at 5-year follow-up, with the corresponding percentages of the class total.

Table III

Independent predictors at diagnosis of uncontrolled asthma at 5-year follow-up, with the corresponding odds ratios (OR) and 95 % confidence intervals (CI)

Predictor	OR	CI
Allergy to pollen	3.25	1.53-6.92
Allergy to cats	2.15	1.14-4.08
Crises or hospitalizations in the year prior to diagnosis	1.13	1.02-1.26
Age at onset of symptoms	0.86	0.76-0.98

mites. This coincided with allergy to pollen in 44 cases (18 %), and to cats in 69 (28 %).

As can be seen in Figure 1, at 5-year follow-up, adequate control of asthma had been achieved by 172 patients (69 %): 84 % of patients with an initial diagnosis of intermittent asthma; 68 % of those with initial mild persistent asthma; and 60 % of those with moderate or severe persistent asthma ($p < 0.01$). According to atopic response adequate control of asthma is more frequent between those not sensitized (by comparison with those sensitized). Adequate control has been achieved by 67 % of patients sensitized to mites and by 87 % not sensitized to mites ($p < 0.05$); by 52 % of those sensitized to pollen and 73 % of those not sensitized to pollen ($p < 0.05$); and 58 % of those sensitized to cats and 73 % of those not sensitized to cats ($p < 0.05$).

The variables shown by univariate analyses to be associated with poor control at 5-year follow-up were severity at diagnosis, poor adherence to treatment, specific allergen immunotherapy, allergy to cats or pollen, younger age at onset of the disease, and the number of crises or hospitalization episodes in the year prior to diagnosis (results not shown). Of these, those shown by multivariate logistic regression analysis to have independent effects were: allergy to cats; allergy to pollen; the number of crises or hospitalization episodes in the year prior to diagnosis; and younger age at onset (Table III). In particular, the risk of non-control was doubled by allergy to cats, and tripled by allergy to pollen.

DISCUSSION

In view of the geographical heterogeneity of the prevalence of childhood asthma[5], it is desirable for factors associated with poor control to be identified for each geographical region. This study aimed to fulfil this need, for the catchment area of our hospital. We did not attempt to determine the prevalence or incidence of childhood asthma in this area, but our data do probably afford a reliable estimate of the distribution of asthma between the sexes; the ratio of 1.83:1, with greater prevalence among boys, is similar to that found in other studies[6-9].

The proportion of patients achieving satisfactory control of asthma has varied widely from study to study. This has probably been largely due to differences among these studies as regards the evaluation of response to treatment, the definition of remission, the age of the patients, criteria for admission to the study, and the length of follow-up. Genetic, environmental and therapeutic differences may also have been involved. The generally satisfactory response of

our patients may have been favoured by their having been managed by the specialists of a hospital Paediatric Allergy and Pulmonology Unit[10-12].

Severity at diagnosis

Our findings agree with those of most other studies[13-15]; (the study by Mazón et al[7] is an exception), in that severity at diagnosis was associated with the persistence of symptoms. Although NIH severity did not emerge as having an independent effect on control in the multivariate analysis, an independent effect *was* detected for the number of crises prior to diagnosis, which is also a measure of severity. This association is coherent with the reported association of severity with bronchial remodelling[16] and with poor lung function in young adulthood[17].

Poor prognosis has also been associated with the recurrence of infections, which are known to be associated with asthmatic crises. In particular, an adverse influence of respiratory syncytial virus has been reported[18,19]. Paradoxically, infections have been reported to protect against or ameliorate allergies[20]. It is also possible that upper airway infections are favoured by asthma, rather than the reverse[21]; certainly, the symptoms of viral infections are more intense and longer-lasting in asthmatic patients than in others[22,23].

The poor prognosis of patients with greater severity at diagnosis suggests that good control of the disease at onset may reduce its effects in later life.

Age of onset

The prognostic implications of age of onset are also unclear. Like Kjellman and Hesselmar[24], we found that earlier age at onset was associated with greater severity, but others have observed the reverse[15,25] and others again no influence at all[7,8,26], while Ulrik et al reported that earlier age at onset worsened prognosis for intrinsic asthma but not for extrinsic asthma[27]. When follow-up has been pursued to adulthood, age of onset has exhibited negative correlation with the risk of relapse in adulthood[26]. That earlier age of onset has unfavourable implications would be in keeping with the suggestion that onset may be initiated by viral infections that lead to alterations in the structure and function of the developing airways[28], since the still-developing lungs of younger patients[29] may be expected to be more susceptible of alteration than those of older patients. Such alterations would explain why, as noted above, the symptoms of viral infections are more intense and longer-lasting in asthmatic patients than in others[22,23].

Atopy

In some studies, atopy has been found to have no influence on the persistence of asthma[8,24,30,31], while in others it has been associated with poor prognosis[7,9,25,32-35]. Since the expression of atopy depends on both genetic factors and exposure to environmental stimuli[19], discrepancies as to the allergens involved in atopy-associated persistence of asthma may be due to both kinds of factor, although differences in environmental exposure seem likely to predominate. For example, persistent wheezing was associated with an atopic response to house dust in New Zealand[26], but with *Alternaria* in Arizona[36].

Of the allergens considered in the present study, only pollen and cats increased the risk of persistence. An atopic response to cats was also found to be detrimental in a study carried out in Hungary[6], although not so in certain other studies[7,26]. The atopy that in the present study most increased the risk of persistence, atopy to pollen, has not previously been reported to have an independent influence on persistence[6,7,26], although its association with poor remission in a univariate analysis in Mazón et al's study[7] suggests that its non-emergence in multivariate analyses may have been due to it being less allergenic than other allergens considered.

Since the persistence of subclinical airway inflammation most probably favours the persistence of asthmatic symptoms[37,38], the relatively poor prognosis for atopic patients is in keeping with reports that they have greater airway inflammation than non-atopic patients, as evaluated by measurement of exhaled nitric oxide[39]. However, we do not know why atopy towards some allergens worsens prognosis while atopy towards others appears not to. This situation calls for prospective studies that include data on exposure and sensitization to a range of different allergens, and on the allergen-specific relationships of exposure and sensitization to the prognosis of asthma. Since the environmental allergen spectrum and the sensitization of the population both vary from one geographical location to another, studies of this kind are required for each relevant geographical unit[40].

CONCLUSIONS

That satisfactory control was achieved for 69 % of the patients included in this study suggests that in our region the prognosis of childhood asthma is fair-

ly favourable, as has been found in most published studies[6,9,41]. In the present case this conclusion is strengthened by it being reasonable to suppose that our patients were in general more severely affected than others in the community; all had been referred to hospital, and most of those who dropped out of the study probably did so because of remission or the persistence of only mild asthma. For the same reason, the high proportion of patients achieving satisfactory control appears to support the utility of specialized asthma units. It is possible, however, that because of these special characteristics of our study group, our findings as regards the predictors of unfavourable outcome may not be generalizable to the community in general. It remains to be seen whether stricter management of patients with the risk factors detected in this study will achieve a reduction in morbidity.

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