

Evaluation of atopy through an expert system: description of the database

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Summary

Background In order to understand the medical decisions taken during the initial visit of a new asthmatic patient, a group of experts designed an expert system which provides conclusions about severity, precipitating factors and treatment. Rules for atopy and the assessment of allergic factors have been discussed and implemented in the expert system. Conclusions about severity have been yet validated using an appropriate methodology.

Objective The aim of this study was to investigate a sample of 471 patients according to conclusions regarding atopy.

Methods A total of 471 cases report forms (CRF) was filled in for adult asthmatic outpatients, seen for the first time in our clinic without emergency situations. Data of each CRF were used by the expert system to draw conclusions. The expert system discerns three patterns for atopy, yes, possible or no. The variables known to reflect different features according to the classification of asthma as atopic or not have been studied. The variables used in the rules for atopy, obviously linked to the conclusion, were not compared. For many medical problem no unique objective solution exists and this is why a group of patients with possible atopy was introduced.

Results Patients with atopy had less severe asthma ($P = 0.01$), a better FEV₁ value ($P = 0.0007$) and showed their first symptoms of asthma earlier ($P = 0.00001$) than patients without atopy.

Conclusions The characteristics of the group studied here are consistent with the literature. This could be considered as an indirect validation of the expert system. Moreover, patients with possible atopy show intermediate findings for these variables and it is possible to suggest a 'dose–effect' relationship.

Keywords: expert system, asthma, atopy

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Introduction

In 1918, Rackemann introduced the distinction between asthma associated with hypersensitivity classified as extrinsic and asthma with no such association classified as intrinsic [1]. Thereafter, several definitions have been proposed. Extrinsic asthma refers to asthma caused by

inhalation of allergen which interacts with IgE bound to high affinity receptors on bronchial mucosal mast cells [2] and intrinsic asthma to cases where an IgE-mediated airway reaction to common allergens is not present. However, mixed asthma has been described; aspirin-intolerant asthma cannot be classified as extrinsic or intrinsic and some patients present coexistent asthma with chronic obstructive lung disease.

The term atopy was introduced by Coca and Cooke in 1923 to describe the clinical manifestations of the

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recognized hypersensitivity of asthma and allergic rhinitis [3]. Atopy is now defined as the predisposition to respond to environmental allergens such as inhaled house dust or grass pollen, with production of specific IgE antibodies. It may manifest clinically as asthma, rhinitis, or conjunctivitis [4]. It does not imply the presence of symptoms and is a description of the immunological reactivity of the subject. Clinical history, skin tests, specific or total IgE antibodies are commonly used to recognize atopy. Nevertheless, the methods cited in the literature to assess the atopic status are very variable [5–8], as discussed by Pepys [9], and there is no recommendation in the guidelines on the management of asthma [10].

Asthma is a complex, multifactorial disease and in order to understand the medical decisions involved during the first visit of a new asthmatic patient, a group of experts designed an expert system which draws conclusions about severity, precipitating factors and treatment. Rules for atopy and the assessment of allergic factors have been discussed and implemented in the expert system. Conclusions about severity have been yet validated with an appropriate methodology [11].

The first aim of this study was to describe the database which has been built up by the experts. Asthmatic patients have been classified according to atopic status as assessed by the expert system. The secondary aim was to indirectly validate the conclusion of the expert system about atopy.

Methods

The expert system has been described previously [11]. Briefly, an expert system is a computer program that uses artificial intelligence to provide advice about problems requiring specialized training; it consists of a knowledge base and an interpreter. The knowledge base is constructed by interviewing experts and by converting their knowledge into production rules. Knowledge is represented using two main categories: static knowledge (i.e. signs, symptoms, diagnoses and their inter-relationships) and dynamic knowledge (i.e. production rules). Elicitation of static knowledge involves the characterization and description of medical concepts used to convey the reasoning processes. We have used 300 medical concepts represented as objects (asthmatic attacks for example) which have properties (e.g. frequency, intensity and timing). The expert's knowledge is represented in 'production rules' which are the inferential statements used by the expert system for reaching decisions. The knowledge base contains 1000 rules. The rules have been devised after discussion with physicians by comparing behaviour of the program with their judgement. When

necessary the rules were modified to improve the program and then tested on new cases.

Concordance between the expert system (ES) and the experts when giving score of severity or precipitating factors was assessed by kappa coefficient. Kappa coefficient was 0.263 for severity [11] and 0.41 for atopy. The concordance was good enough to use the conclusions of the expert system. The ES was designated in order to answer questions asked during the first consultation with an adult asthmatic patient. It runs on a Macintosh and uses an Hypercard interface.

A total of 471 adult asthmatic patients was prospectively enrolled and their data collected. The diagnosis of asthma was made by a physician during the first examination according to the ATS definition [12]. Patients were examined by the experts who provided individual and standardized case report form (CRF) for each patient. All subjects were outpatients and no patients requiring emergency treatments were involved.

The experts had to record all clinical findings, results of pulmonary function and biological measurements (if available) for each patient on the CRF [11] which had been produced by the designers of the expert system.

Clinical data including the results of pulmonary function tests are necessary to reach a conclusion but some data are optional such as: blood eosinophilia, sinus and chest x-rays, IgE and skin-prick test (SPT). Since the expert system was designed to reflect every day clinical practice, it is able to draw its conclusions without such additional information; however, the more parameters it receives the more precise is the conclusion given. The expert system has been produced in order to formalize medical decisions concerning asthma and it has to be able to make a conclusion even if some biological data are missing.

When indicated by the expert, SPT were conducted for common aero-allergens (house dust mite, moulds, cat and dog dander, pollens). Codeine phosphate (9%) was used as a positive control and a negative control test was performed using the diluent to discard false positive results. SPT were considered strongly positive if the area of the weal was greater than the control, weakly positive if positive but smaller than the control [13]. If the weal induced by the allergen had a diameter of 1 mm or more but smaller than the control, it was considered as weak positive.

The results of a Phadiatop assay, which include major aero-allergens such as house dust mites, animal danders, grass pollens and moulds, were available for some patients. It provides clearly positive or negative results. Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were measured on a dry wedge spirometer Jaeger Flowscreen. Predicted values for

Table 1. Rules for atopy

A subject is considered to be atopic if (291 patients):

- a) one highly positive skin test: used for 245 patients,
- b) and/or two weak positive skin test: used for 44 patients,
- c) positive phadiatop (and no a nor b): 15 were positives and phadiatop was used twice by the ES to conclude atopy.

Possible atopy if (128 patients):

- a) one weak positive skin test: used for 18 patients,
- b) or negative skin test and negative phadiatop and personal or familial (first degree relatives) previous history of:
 - seasonal rhinitis: used for 75 patients,
 - or seasonal conjunctivitis: used for 17 patients,
 - or atopic eczema: used for 18 patients,
 - or urticaria, or Quinke's oedema: not used.

No atopy if (52 patients):

negative SPT and negative phadiatop and absence of personal or familial (first degree relatives) previous history of:

- seasonal rhinitis,
- or seasonal conjunctivitis,
- or atopic eczema.

FVC, FEV₁ [14] were calculated using the Quanjer regression.

Reversibility of FEV₁ was measured 20 min after inhalation of salbutamol (200 µg) for the patients who had not taken a bronchodilator for 4 h prior to the medical interview. Reversibility of FEV₁ and FVC was expressed in two ways: as an absolute change (mL) from the pre-bronchodilator value, and as a percentage of the predicted value.

We considered the patients who were smokers the day of the medical interview or who had been previously smokers as current smokers, and all the others were considered as non smokers.

The atopic status was evaluated; according to the ES, each patient was classified as having either asthma and atopy (A), or asthma with possible atopy (PA), or asthma without atopy (NA). The decision rules for atopy are given in Table 1. The rules have been acquired after discussion with experts physicians by comparing the program behaviour with their judgement. Some patients with PA have been individualized because at the time of the examination certain biological results were not available (Phadiatop, skin-prick tests) or because it was difficult to incriminate or reject atopy with certainty. This was the case for expert physicians when SPT were negative with a previous history of seasonal rhinitis or when there was only one weak positive SPT.

Variables under study were known to share different features according to the classification of asthma as atopic or not have been studied [2]. The duration of asthma, the age at onset of asthma, the lung function, the distribution of sex, of smokers, the previous familial history of asthma (first degree relatives) were specified on the CRF, and the severity of the disease was compared. The conclusions of the expert system for severity is scored from 1 to 5, the most severe being 4 and 5. Assessment of severity takes into account clinical features, instability of the disease, pulmonary function testing, current treatment and is computed by the expert system. The variables used in the rules for atopy (Table 1), obviously linked to the conclusion, were not compared. There is no common variable used in the rules for atopy and severity, so it was possible to study the distribution of severity according to the conclusions about atopy.

The database contains 300 variables for each of the 471 patients. In the first step we looked for missing data required for the atopy rules and every quantitative variable used in this study was checked for normality. Results are given as mean and standard deviation for normally distributed data and as median, 25th and 75th percentiles for abnormally distributed data. ANOVA (one or two ways) and Scheffe's contrast have been used to compare normally distributed data and Kruskal–Wallis test for non normally distributed data. The chi-squared test was used to compare percentages. Kendall's correlation coefficient was used to check for any relationship between quantitative data. It has been performed on Macintosh PC using Statview IV software.

Results

A total of 471 CRF was analysed using the expert system and 291 patients were considered as A, 128 as PA and 52 as NA.

The median age at onset of asthma for A, PA and NA patients was different ($P = 0.00001$), being 15, 29 and 39 years respectively (Fig. 1). The sex ratio and the percentage of smokers were similar amongst the three groups. Previous familial history of asthma (Table 2) listed 37.8% of the patients in the A group, 36.7% in the PA group and 19.2% in the NA group ($P = 0.03$). Median duration of asthma (Table 2) was the same for A, PA, NA whereas the severity (Fig. 2) was scored 4 or 5 for 21.9%, 35.2% and 48% of the patients respectively ($P = 0.01$). The mean FEV₁ value (Fig. 3) as a percentage of the predicted value was lower ($P = 0.0007$) in the patients with NA (67%) than in the PA group (74.9%) and in the A group (80%). The effect of smoking and atopy on FEV₁ values were analysed using a two-way

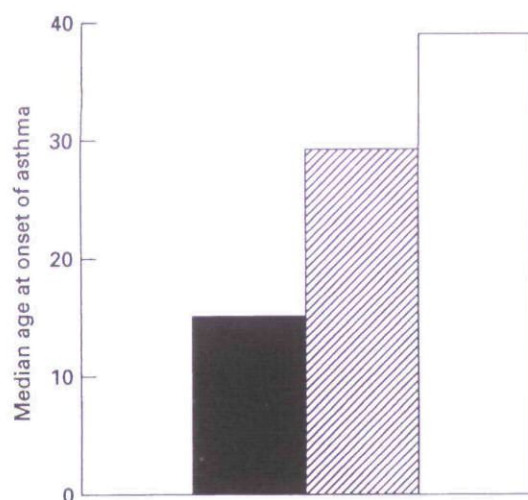


Fig. 1. Median age at onset of asthma for patients with atopy (■), possible atopy (▨), and without atopy (□); $P = 0.00001$.

ANOVA: the 'atopy effect' was significant ($P = 0.003$) when there was no 'smoking effect' ($P = 0.15$) and no interaction ($P = 0.07$).

Changes in FEV_1 values after taking bronchodilators is expressed in absolute terms and as proportion of predicted values (Table 2). Reversibility, expressed as a percentage of predicted values, was correlated with baseline FEV_1 values ($T = -0.197$, $P < 0.0601$) whereas reversibility expressed in absolute term was not ($P = 0.5$). In both situations, reversibility was significantly higher in the NA patients (Table 2).

The analysis of missing data at the time of compilation showed that all but one patient with A had SPT, 30% and 27% of patients with PA and NA respectively didn't have SPT.

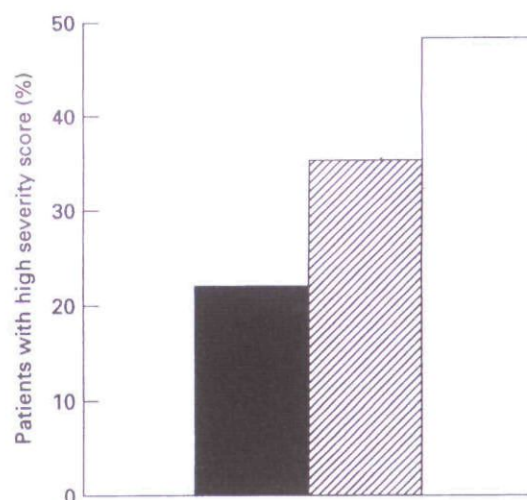


Fig. 2. Percentage of patients with high severity score (4 and 5 according to the ES) for patients with atopy (■), possible atopy (▨), and without atopy (□); $P = 0.01$.

In the NA group, the patients who had and had not undergone SPT differed in their age (median: 48 years vs 60 respectively, $P = 0.005$), the reversibility of FEV_1 values expressed as absolute change from baseline value (median: 516 mL vs 290 respectively, $P = 0.03$) and there was not statistically significant difference for the duration of asthma ($P = 0.07$), the age at onset of asthma ($P = 0.6$), the FEV_1 values expressed as a percentage of predicted values ($P = 0.35$), the reversibility of FEV_1 values expressed as a percentage of predicted values ($P = 0.08$), the severity ($P = 0.3$), the tobacco consumption ($P = 0.4$) and previous familial history of asthma ($P = 0.4$).

In the PA group, the patients who had and had not

Table 2. Characteristics of asthmatics patients

	Total sample <i>n</i> = 471	A <i>n</i> = 291	B <i>n</i> = 128	C <i>n</i> = 52	<i>P</i>
Men %	47	49.1	40.6	55.7	0.12
Smokers %	19.9	20	18	21	0.9
Duration of asthma (years)	12	12	10	10.5	0.13
(Median)	(4,20)	(5,21)	(3,20)	(2,21)	
Familial previous history of asthma %	36	38	37	19	0.03
R %	10	10	9.5	13.5	0.02
(Median)	(6,16)	(6,16)	(5,13)	(9,21)	
R mL	330	300	300	400	0.02
(Median)	(200,508)	(200,520)	(150,400)	(234,615)	

A. Atopy. B. Possible atopy. C. Absence of atopy. R is reversibility of FEV_1 .

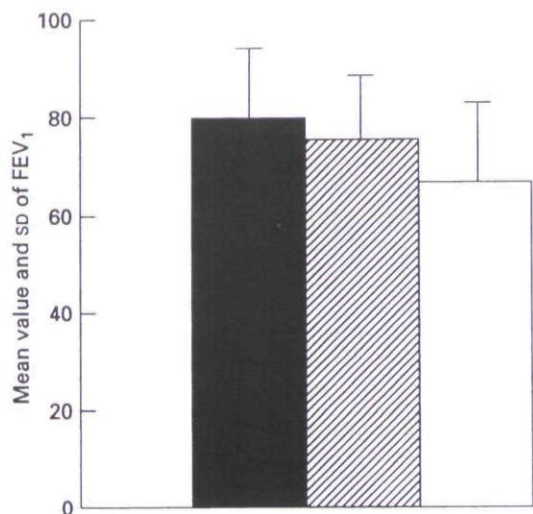


Fig. 3. Mean FEV₁ (% predicted) for patients with atopy (■), possible atopy (▨), and without atopy (□); $P = 0.0007$.

undergone SPT differed in the age at onset of asthma (median: 32 years vs 24 respectively, $P = 0.01$), the duration of asthma (median: 11 years vs 19 years, $P = 0.002$); there was not statistically significant difference for age ($P = 0.9$), FEV₁ values expressed as a percentage of predicted values ($P = 0.85$), reversibility of FEV₁ values expressed as absolute change from baseline value ($P = 0.79$), reversibility of FEV₁ values expressed as a percentage of predicted values ($P = 0.08$), severity ($P = 0.6$), tobacco consumption ($P = 0.8$) and previous familial history of asthma ($P = 0.23$).

Discussion

The analysis of this group of asthmatic patients, according to the conclusions of the expert system concerning atopy, show that A patients are younger and present less severe asthma than NA patients. In a third group, patients were classified as PA because some key data were missing at this first medical interview to allow atopy to be identified definitively and because of a lack of agreement in the definition of atopy.

Problems of definition in medicine are common and there is not a general agreement on the way to define and to assess atopy. Nelson who used a different skin-test method showed that the weal size necessary for 99% specificity varied from 2 mm to 5.5 mm [15]. Cookson [7], in his study about inheritance of atopy, used the criteria described in the study of Stenius [4], with a positive result for the SPT if the weal is more than 1 mm greater than negative control. Bryant [16] showed that to measure the weal size had a clinical support; he found a relationship

between the size of the weal and the threshold dose of allergen able to give a positive bronchial provocation test reaction. Burrows [17] graded each test on a scale after subtraction of the size of the control and found a trend for asthma prevalence to increase with the value of the skin-test index. Others [18,19] assessed atopic status by the number of positive SPT reactions. Less often, total serum IgE [20], concomitant rhinitis or eczema are used as indices.

Whatever the difficulty to assess the atopic status of one patient, it was necessary to build rules for the expert system. Even though there are different ways of analysing SPT results found in the literature, atopy remains the most common diagnosis. Therefore, the expert physicians involved in the development of the expert system decided to use clearly positive SPT to conclude atopy. Vervloet *et al.* [21] studied reliability of respiratory symptoms to diagnose atopy and demonstrated that the predictive value of each symptom suggestive of atopy was quite low. So a possible atopy group was introduced on the basis of one weak positive skin-test or personal previous history of rhinitis or conjunctivitis. Other reasons for introducing a PA group were that not all the patients could undergo SPT on the day of the first consultation. Therefore, the PA group is constituted with patients for whom it was not possible to conclude about atopy for medical or pragmatic reasons.

The expert system classified 128 (27%) patients as PA. Among these patients, 30% did not have skin-prick tests because they had an anti-histaminic treatment or a negative control with phosphate codeine. They were younger at the time at onset of asthma and perhaps the physician considered that the probability for these patients to be atopic was so high that SPT were not useful; 27% of the NA patients didn't have SPT. These had a median age of 60 years and probably the physician considered that skin-prick tests were not useful for these older patients [21].

Intrinsic asthma is generally known to be more severe [2,22] than extrinsic asthma. The severity score used by the expert system and validated in a previous study [11] gave results which were in keeping with the literature. Moreover, the proportion of patients with a high severity score in the PA group is intermediate between A and NA group as if there was a negative correlation between severity of asthma and the degree of atopy. The results are similar for age at onset of asthma, however, Pepys found a significant negative correlation between age at onset and degree of atopy [19].

Reversibility after a bronchodilator supports a clinical diagnosis of asthma and indicates that bronchodilator therapy is beneficial. In this study, reversibility of FEV₁ values after beta agonist had to be demonstrated

within the previous 6 months, the day of the consultation or the month following the consultation.

One method of expressing change in FEV₁ values after bronchodilator is as a proportion of the predicted value and an enhancement of 15% is needed to meet the condition of reversibility. However, several studies have established that a post bronchodilator increase in FEV₁ values of more than 190 mL exceeds the approximate 95% range of increases expected by chance in adults and implies reversibility [23–25].

The definition of reversibility is still controversial, and in our sample of asthmatics, 111 patients (28.7%) enhanced their FEV₁ value of 15% or more and 295 patients (76%) of 190 mL or more. Reappraisal of the criteria used and their limitations is required. Moreover, the dose of beta agonist used to measure reversibility is not standardized.

Cigarette smoking, which is known to be the most important factor for the development of chronic obstructive pulmonary disease (COPD), was similar in the three groups (20%) of asthmatic patients and had no effect on FEV₁ values. The mean reason for the absence of a 'smoking effect' could be the low intensity of smoking (median of 4 pack-years for 20% of patients considered as smokers, without significant difference between the A, PA, NA group) in this sample of asthmatic patients. The absence of statistic interaction means that whatever the level of atopy, cigarette smoking has the same effect on FEV₁. Therefore, the differences observed among these three groups may not be due to inclusion of patients with COPD in the NA or PA group.

The PA group is different from the A and NA groups and curiously, intermediate for: the age at onset of asthma, the severity of asthma and the FEV₁ values. Nevertheless, with the follow-up study which is going on and with additional data as results of phadiatop or SPT for all patients, the conclusion about atopy for some of them will be modified. It remains difficult to say if the PA group is just the result of a misclassification because of a lack of data for these patients or if we find intermediate results as if there was a 'dose-effect' relationship for atopy and data as the age at onset of asthma, the severity of asthma and the FEV₁ value.

A and NA patients show different clinical features and it stays now difficult to say if intrinsic asthma must be considered as a separate entity or if extrinsic and intrinsic asthma share a common basis modified by atopy.

Even if the rule for atopy used by the expert system is only similar than those generally used, the study of this sample of asthmatic patients give results which are concordant with the literature and this could be considered as an indirect validation of the expert system.

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