

Severity of asthma in skin test-negative and skin test-positive patients

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The standardized records of 144 asthmatic patients have been analyzed to determine whether the severity of their condition was correlated with the presence or absence of positive intradermal skin test reactions to a panel of seven allergen extracts (dust, feathers, Alternaria, Hormodendrum, mixed tree pollen, mixed grass pollen, and ragweed pollen). The skin tests were totally negative in 71 of the subjects, whereas in 73 subjects there was a strongly positive response to two or more allergens. The skin test-negative patients were older than the skin test-positive ones and had a shorter duration as well as a later onset of asthma. Also, they had lower serum-IgE levels and a lower frequency of a family history of atopic disease. Moreover, the skin test-negative group lost more time from their normal activities, required more visits to their doctor as a result of asthma, and were more frequently treated with oral corticosteroids. They additionally had greater air trapping on pulmonary function tests. However, when the groups were adjusted for the discordance in their age and duration of asthma, they tended to converge in the level of the variables that described the severity of their asthma. Thus the severity of asthma was found to be relatively similar in skin test-negative and skin test-positive patients. (J ALLERGY CLIN IMMUNOL 75:313-19, 1985.)

For many years patients with an allergic component to their asthma have been regarded as having a better prognosis than so called "intrinsic" or nonallergic asthmatic patients. Unger¹ surveyed a group of asthmatic patients and reported that 29% of those who were "extrinsic" but only 5% of the "intrinsic" ones had been completely symptom free for at least 1 yr before the time of the survey. Similarly, Pearson² and Ogilvie³ found allergic asthmatic subjects to have milder symptoms than nonallergic ones. By contrast, Rackeman and Edwards⁴ reported that among asthmatic patients who were reviewed 20 yr after having been observed in childhood, a higher proportion of nonallergic than allergic subjects were observed to have become symptom free (62% versus 24%). However, it is further known that asthmatic patients having an important allergic element tend to develop their

Abbreviations used

VC: Vital capacity
 $\dot{V}_{50}$: Maximum expiratory flow rate at 50% VC
 $\dot{V}_{25}$: Maximum expiratory flow rate at 25% VC
FRC: Functional residual capacity
TLC: Total lung capacity
RV: Residual volume

disease at a younger age than those in whom this factor is less evident.⁵ Thus differences could readily occur in the age or duration of disease in the asthmatic subgroups compared in the foregoing studies, and this could confound the analysis on the basis of presence or absence of allergy. In support of this is the finding by Hanneuse et al.⁶ that the proportion of corticosteroid-dependent asthmatic patients increases with age and is similarly distributed among "allergic" and "nonallergic" cases.

The allergic or extrinsic asthmatic patient usually has been defined in these and other studies on the basis of symptom provocation by known external agents associated with an immediate wheal-and-flare skin test reaction to the suspected offending mate-

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rial.^{7,8} In the present article we have compared the characteristics of asthmatic patients who were categorized on the basis of having either totally negative or strongly positive skin test reactions to at least two materials from a standard panel of seven skin test reagents. The two groups also differed dramatically in other variables including their serum-IgE levels and personal and family history of hay fever and eczema and exacerbation of symptoms by animals. The skin test-negative group was found to demonstrate a number of features of having more severe asthma than the skin test-positive group. However, these differences were appreciably diminished when adjustment was made for differences between the groups in age and duration of asthma.

METHODS

Patients

The records of 482 asthmatic patients attending the clinic of The Gage Research Institute between 1973 and 1980 were reviewed for this study. These patients were referred mainly by family physicians practicing within a 100-mile radius of Toronto. Subjects were considered to have asthma if they had a history consistent with episodic airway obstruction, if diffuse expiratory wheezes were heard on auscultation of the chest, and if they demonstrated a change of at least 15% in their spirometric measurements after the inhalation of 400 μ g of salbutamol. Of the 144 subjects on whom this report is based, no wheezes were heard in 10 subjects, and no short-term changes in the level of airway obstruction were observed in a separate group of nine subjects. These latter 19 patients were equally distributed among the skin test-positive and skin test-negative patients.

Documentation

All patients observed in the asthma clinic were assessed by clinical immunologists and respirologists from teaching hospitals affiliated with the Faculty of Medicine of the University of Toronto. A standardized format was used consisting of a medical questionnaire, physical examination, skin tests, chest radiograph, electrocardiograph, pulmonary function tests, urinalysis, peripheral blood hematologic assessment, and determination of serum immunoglobulin and α_1 -antitrypsin levels. The computer-ready medical questionnaire was completed by the physician and collected the details of a full medical, occupational, and family history. (Copies of the questionnaire are available on request.)

Historical assessment of severity

The severity of asthma was assessed from eight questionnaire variables and from the pulmonary function results. The questionnaire collected information on the frequency of asthmatic symptoms (graded 1 to 7 according to a stepwise range of symptom frequencies beginning with less often than a few days per year and extending to constant symptoms); activity limitation (graded in steps from 1 to 9

starting from the capacity to undertake vigorous activity normal for age and build and extending to the maximum limitation of being confined to bed because of breathing difficulties); days per year of time loss from normal activities caused by asthma during the preceding year; number of visits to the doctor for treatment of asthma during the preceding year; number of days admitted to hospital for treatment of asthma during the preceding year; and requirement for each of three medications expressed as number of days the respective drug was required during the preceding year (oral bronchodilator, inhaled bronchodilator, and oral corticosteroid).

Pulmonary function tests

Maximal expiratory flow volume curves were performed before and 20 min after four puffs (100 μ g each) from a salbutamol inhaler with the use of a wedge spirometer equipped with a 1-sec time marker. Replicate curves for a given subject were superimposed at total lung capacity, and the maneuver repeated until two tracings were obtained that corresponded within 5% both for FVC and for flow over the lowest 70% of vital capacity. The best curve on the basis of acceptable effort, with the largest VC and flow rate, was used to measure FEV₁, the FVC, $\dot{V}_{50}$, and $\dot{V}_{25}$. These measurements were expressed in BTPS as percent of normal predicted values with use of the prediction formula of Schoenberg et al.⁹ for FVC, FEV, $\dot{V}_{50}$, and $\dot{V}_{25}$. FRC was measured by helium dilution (Collins modular lung analyzer, Warren E. Collins, Inc., Braintree, Mass.), which enabled the calculation of other subdivisions of the lung volume. The predicted values for TLC and RV were from Goldman and Becklake.¹⁰

Skin tests

Intradermal skin tests were performed by use of the following seven common allergen extracts (Hollister Stier Laboratories, Toronto, Canada): house dust mixture (1000 PNU/ml), tree pollen mix (500 PNU/ml), grass pollen mix (500 PNU/ml), ragweed pollen mix (500 PNU/ml), *Hormodendrum* (1000 PNU/ml), *Alternaria tenuis* (1000 PNU/ml), and feather mix (1000 PNU/ml). An eighth test was performed with control solution. Additional tests were performed with other allergens such as animal danders as indicated by the individual patient's history. The results were read after 20 min. A negative response was defined as a mean wheal diameter smaller than or equal to the control response. A 4+ response was defined as a wheal more than 10 ml larger than the control with the presence of pseudopodia. All patients were routinely instructed to stop any antihistamine medications for 24 hr before undergoing the skin tests.

For the purposes of this study, subjects with negative responses to all seven allergens were considered to be skin test negative, whereas those having two or more 4+ reactions were assigned to the skin test-positive group. Patients who had a positive reaction to an additional allergen but would otherwise have been classified skin test negative were excluded from consideration, as were those who had only small skin test responses intermediate between negative

TABLE I. Comparison of asthmatic subjects having negative or positive skin test reactions

	Skin test negative	Skin test positive	<i>p</i> Value*
No. of subjects	71	73	
% M	54	45	
Age	50 ± 16†	33 ± 14	0.0001
Age of asthma onset	38 ± 18	15 ± 15	0.0001
Duration of asthma (yr)	12 ± 16	18 ± 13	0.02
Current smokers (%)	17	14	
Aggravation by cold air (%)	68	71	
Aggravation by animals (%)	11	64	0.0001
Hay fever ever (%)	4	55	0.0001
Eczema ever (%)	6	27	0.006
Family asthma (%)	38	63	0.003
Family hay fever (%)	24	58	0.0001
IgE (natural log IU/ml)	4.0 ± 1.3	5.7 ± 1.3	0.0001
Activity limitation scale‡	2.5 ± 1.7	1.7 ± 1.2	0.0004
Asthma frequency scale§	5.4 ± 1.4	4.8 ± 1.4	0.01
Doctor visits/yr	11 ± 13	7 ± 9	0.02
Time loss (days/yr)	38 ± 76	14 ± 39	0.02
Hospital (days/yr)	0.7 ± 1.5	0.5 ± 1.1	
Oral bronchodilator (days/yr)	160 ± 158	134 ± 151	
Inhaled bronchodilator (days/yr)	131 ± 152	144 ± 156	
Oral corticosteroid (days/yr)	134 ± 156	64 ± 129	0.004
FEV ₁	69 ± 28	76 ± 26	
$\dot{V}_{max_{50}}$	50 ± 34	52 ± 30	
$\dot{V}_{max_{25}}$	49 ± 35	45 ± 27	
FVC	90 ± 24	97 ± 19	
FRC	108 ± 30	95 ± 25	0.01
TLC	104 ± 16	100 ± 14	
RV	121 ± 55	101 ± 39	0.02

**p* Values were obtained by chi square and *t* tests. A blank represent a *p* value more than 0.05.

†Mean ± standard deviation.

‡Activity limitation scale is graded in steps from 1 to 9 starting from the capacity to undertake vigorous activity and extending to the maximum limitation of being confined to bed because of breathing difficulties.

§Asthma frequency scale is graded from 1 to 7 according to a stepwise range of symptom frequencies beginning with less often than a few days per year and extending to constant symptoms.

||All pulmonary function results are expressed as percent of normal predicted values.

and 4+. Approximately 90% of the patients had perennial symptoms, and thus those in the skin test-positive group were presumed to have symptoms during exposure to the corresponding allergens. Of 482 records reviewed 71 patients were classified as skin test negative, 73 patients as skin test positive, and 338 patients were excluded from further study on the basis either of the foregoing or of not having undergone the full battery of skin tests or having only positive responses intermediate between negative and 4+.

Serum IgE

Serum-IgE levels were determined by use of the PRIST method.¹¹

Statistical analysis

Statistical analysis was performed with the use of the facilities of the University of Toronto Computer Centre with

packages of the Statistical Analysis System. The tests performed included paired and unpaired chi square and *t* tests and analysis of covariance.

RESULTS

A total of 71 skin test-negative and 73 skin test-positive asthmatic patients were included in this study. The credibility of these skin test groupings was supported by several observations (Table I), such as the skin test-positive subjects demonstrating a considerably higher level of serum IgE. Also, significantly more of the skin test-positive patients reported aggravation of their condition by animal exposure, whereas both groups noted a similar frequency of aggravation by cold air and other nonspecific factors. Moreover, the skin test-positive group had a consid-

TABLE II. Comparison of skin test-negative or skin test-positive asthmatic subjects by analysis of covariance adjusting for age and duration

	Skin test negative	Skin test positive	<i>p</i> Value
No. of subjects	71	73	
IgE (natural log IU/ml)	4.2*	5.6	0.0001
Activity limitation scale†	2.2	1.9	
Asthma frequency scale‡	5.3	4.9	
Doctor visits/yr	11	7	
Time loss (days/yr)	35	16	
Hospital (days/yr)	0.7	0.6	
Oral bronchodilator (days/yr)	154	140	
Inhaled bronchodilator (days/yr)	148	127	
Oral corticosteroid (days/yr)	121	77	
FEV ₁ §	73	73	
$\dot{V}_{max_{50}}$	58	46	0.05
$\dot{V}_{max_{25}}$	56	40	0.01
FVC	91	97	
FRC	104	99	
TLC	102	102	
RV	118	104	

*Least squares mean.

†Activity limitation scale is graded in steps from 1 to 9 starting from the capacity to undertake vigorous activity and extending to the maximum limitation of being confined to bed because of breathing difficulties.

‡Asthma frequency scale is graded from 1 to 7 according to a stepwise range of symptom frequencies beginning with less often than a few days per year and extending to constant symptoms.

§All pulmonary function results are expressed as percent of normal predicted values.

erably higher prevalence of a personal and a family history of hay fever and eczema and a family history of asthma.

The skin test-negative subjects were appreciably older than the others and had a later age of onset with a correspondingly shorter duration (Table I). Both groups were well matched on smoking experience. The skin test-negative group demonstrated a number of differences suggesting the presence of more severe asthma than was observed in the skin test-positive group including significantly more frequent symptoms of asthma, as well as greater exercise limitation, time loss from normal activity, need for physician visits, and use of oral corticosteroids. Moreover, the skin test-negative group had more marked air trapping than the others as was indicated by the presence of a significantly higher FRC and RV.

We considered the possibility that the severity of asthma in the skin test-negative group might be either overestimated as a result of their older age or underestimated in relation to their shorter duration of asthma. Two approaches were used to explore these possible opposite confounding effects of age and duration. The first used analysis of covariance to simultaneously adjust for differences in both age and duration between the two groups. Correction for age

alone did not improve the balance between the groups for duration or age of onset of asthma (age-adjusted duration of asthma for skin test-negative group 9 yr versus 21 yr for skin test-positive group; age-adjusted age of onset for skin test-negative group 32 yr versus 20 yr for skin test-positive group). The addition of pack years of smoking to the covariates did not materially change the results from those obtained by only adjusting for age and duration of asthma. Among the age- and duration-adjusted severity variables, the only significant differences detected were in the flow rates, which demonstrated higher values among the skin test-negative than among the skin test-positive subgroups (Table II). There was a persisting trend for other indicators of severity, such as activity limitation and corticosteroid usage, to remain worse among the skin test-negative group, but these differences did not reach a statistically significant level.

The second method used to correct for the confounding effects of age and duration of asthma was to confine the comparison of the two groups to only those subjects who could be matched on these variables. However, the pairs were additionally matched on sex and smoking experience in order to avoid the introduction of additional sources of bias. We were able to match on age within an averaged difference

TABLE III. Comparison of skin test-negative or skin test-positive asthmatic subjects matched by age, duration, sex, and smoking experience

	Skin test negative	Skin test positive	<i>p</i> Value*
No. of subjects	30	30	
% M	37	37	
Age	43 ± 17 [†]	42 ± 15	
Age of asthma onset	29 ± 15	29 ± 16	
Duration of asthma (yr)	14 ± 16	13 ± 15	
Current smokers (%)	13	13	
Hay fever ever (%)	10	70	0.0003
Eczema ever (%)	13	13	
Family asthma (%)	50	50	
Family hay fever (%)	30	57	
IgE (natural log IU/ml)	4.1 ± 1.2	5.2 ± 1.3	0.003
Activity limitation scale [‡]	2.3 ± 1.5	2.2 ± 1.6	
Asthma frequency scale [§]	5.5 ± 1.2	4.9 ± 1.5	0.05
Doctor visits/yr	12 ± 14	10 ± 15	
Time loss (days/yr)	27 ± 53	19 ± 65	
Hospital (days/yr)	0.7 ± 1.6	0.5 ± 0.9	
Oral bronchodilator (days/yr)	188 ± 157	148 ± 162	
Inhaled bronchodilator (days/yr)	166 ± 169	97 ± 142	
Oral corticosteroid (days/yr)	123 ± 151	107 ± 163	
FEV ₁	73 ± 31	77 ± 28	
Ṽ _{max50}	58 ± 40	52 ± 32	
Ṽ _{max25}	58 ± 44	47 ± 28	
FVC	93 ± 21	99 ± 18	
FRC	103 ± 25	100 ± 24	
TLC	104 ± 14	103 ± 14	
RV	114 ± 42	104 ± 38	

**p* Values were obtained by paired chi square and *t* tests. A blank represents a *p* value more than 0.05.

[†]Mean ± standard deviation.

[‡]Activity limitation scale is graded in steps from 1 to 9 starting from the capacity to undertake vigorous activity and extending to the maximum limitation of being confined to bed because of difficulties.

[§]Asthma frequency scale is graded from 1 to 7 according to a stepwise range of symptom frequencies beginning with less often than a few days per year and extending to constant symptoms.

^{||}All pulmonary function results are expressed as percent of normal predicted values.

of 1.2 yr and on duration within an averaged difference of 0.3 yr (see Table III). The 30 matched pairs demonstrated a similar difference in their history of hay fever and in their serum-IgE level as observed in the full population (Table I). Also, the skin test-negative group continued to demonstrate a higher frequency of asthma symptoms (*p* 0.05) but had a further equalizing of other severity variables on comparison with the skin test-positive group over that observed with analysis of covariance (Table II).

DISCUSSION

Our approach in this study has been to compare the severity of asthmatic patients stratified according to whether or not they had positive skin test reactions. In order to maximize the contrast between these groups, we included patients in the positive category

only if they had two or more strongly positive reactions (mean number of positive reactions = 3.6) and patients in the negative group only if all tests to the standard panel of antigens were totally negative. This method of stratification appears to have been meaningful, since the two assembled groups were found to differ in the expected manner in their characteristics of atopy (Table I). Our decision to take this approach was based on preliminary tests of our data, in which we found that groups of asthmatic patients who had skin test responses not exceeding 3+, 2+, or 1+, respectively, demonstrated a gradual shift in their characteristics from those having 4+ results to others who had entirely negative responses. The assumption would generally tend to be made that the skin test-positive subjects were extrinsic asthmatic patients, and the skin test-negative patients were intrinsic. This

would imply that the first group had symptoms related to allergens that were responsible for their positive skin reactions, whereas the second group were non-reactive both to the test antigens and to other potential allergens. Although there would undoubtedly be individual exceptions to either assumption, these two groups likely represent a reasonable approximation of extrinsic and intrinsic asthmatic patients.

The possibility could be raised that the difference in atopic characteristics between the skin test-positive and skin test-negative subjects (Table I) was an artifact of the differences in their mean age, since the prevalence of positive skin test reactions and the level of serum IgE are known to diminish with age.⁶ However, the differences in most atopic characteristics were retained between the two groups even after adjustment was made for age (Tables II and III).

The skin test-negative subjects demonstrated features of more severe asthma than the skin test-positive ones (Table I). This finding conforms with that reported previously in comparisons of intrinsic and extrinsic asthmatic patients.^{2,3} In our subjects the difference in severity between the two groups could not be explained on the basis of the asthma being only seasonal in the skin test-positive group, since both groups reported a similar frequency of perennial symptoms (skin test-negative group, 90% versus skin test-positive group, 89%). The differences in the severity characteristics became smaller when the comparison was repeated with adjustment being made for age and duration of asthma (Table II). The adjusted flow rates for the skin test-negative group were higher than the skin test-positive group, but this was likely explained on the basis of their having a higher residual volume with an equal total lung capacity. Consequently, the flow rates of the skin test-negative group were calculated at a higher lung volume relative to those of the skin test-positive group. Otherwise, the adjusted severity characteristics of the skin test-negative subjects continued to reveal a trend in the direction of being worse, although these differences were not statistically significant. It would have taken a group size of 96 to achieve a significant level of 0.05 for oral corticosteroid usage.

All severity differences between the skin test-negative and skin test-positive subjects further converged when the comparison was confined to those who could be matched on the basis of age and duration of asthma, although they continued to differ significantly in their frequency of asthma symptoms (Table III). The subjects who were dropped from this analysis consisted of an excess of older skin test-negative patients and of younger skin test-positive ones for whom insufficient matches were available in the opposite groups.

However, the matched groups represented an evenly distributed range of ages from 5 to 77 yr.

The question remains as to which of the two methods of adjusting provided the most reliable basis for comparing the groups. Both analysis of covariance and matched-pair analysis must be used with caution when there is a lack of parallelism between the adjusting variable and the dependent variable in the groups being compared. However, a statistically significant difference in the slopes between the two groups should not by itself be the criterion of non-parallelism because tests of significance are dependent on sample size. With a sufficiently large sample the smallest departure from parallelism would be declared significant. In the foregoing data set the only relationships that deviated significantly from parallel were between age and oral corticosteroid use (p 0.05) or $\dot{V}_{25}$ (p 0.03) and between duration of asthma and time loss (p 0.02). In the presence of an appreciable lack of parallelism, the adjusted means obtained for the dependent variable through either covariance analysis or matching become influenced by the mean of the adjusting variable. Thus the disparity in the values for time loss, oral corticosteroid use, and $\dot{V}_{25}$ in Tables II and III can be explained on the basis of the matched sample being on the average older than that compared by covariance analysis (43 versus 41 yr) and having a shorter duration of asthma (14 versus 15 yr), since the differences in these variables between the skin test-negative and skin test-positive groups tend to diminish with age and increase with duration. Although matching and covariance analysis produce a generally similar result, clinicians are more comfortable with the use of matching, since the means obtained are based on actual data rather than being estimated through a process of statistical adjustment.

Thus we conclude that the severity of asthma is relatively similar in skin test-negative and skin test-positive patients when the groups are balanced on age and duration of asthma. This statement can likely be extended to intrinsic and extrinsic asthmatic patients.

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REFERENCES

1. Unger L: Bronchial asthma. Results of treatment in 207 patients under observation for a period varying from one to thirteen years. *J ALLERGY* 7:364, 1935
2. Pearson RSB: Natural history of asthma. *Acta Allergol* X11:277, 1958
3. Oglivie AG: Asthma: a study in prognosis of 1000 patients. *Thorax* 17:183, 1962
4. Rackeman FM, Edwards MC: Asthma in children. A follow-up study of 688 patients after an interval of twenty years. *N Engl J Med* 246:815, 1952

5. Pearson RSB: Asthma—allergy and prognosis. *Proc Roy Soc Med* 61:467, 1968
6. Hanneuse Y, Delespesse G, Hudson D, De Halleux F, Jacques JM: Influence of ageing on IgE-mediated reactions in allergic patients. *Clin Allergy* 8:165, 1978
7. Turner-Warwick M: Provoking factors in asthma. *Br J Dis Chest* 65:1, 1971
8. Sibbald B: Extrinsic and intrinsic asthma: influence of classification on family history of asthma and allergic disease. *Clin Allergy* 10:313, 1980
9. Schoenberg JB, Beck GJ, Bouhuys A: Growth and decay of pulmonary function in healthy blacks and whites. *Respir Physiol* 33:367, 1978
10. Goldman HI, Becklake MR: Respiratory function tests—normal values at median altitudes and the prediction of normal results. *Am Rev Respir Dis* 79:457, 1959
11. Kjellman N-IN, Johansson SGO, Roth A: Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). *Clin Allergy* 6:51, 1976

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