

Respiratory pathophysiologic responses

Findings before the diagnosis of asthma in young adults

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Background: Asthma is a poorly understood disease. Risk factors are not established, and the natural history of the disease is unknown.

Objective: Using subjects of a community-based study, we have prospectively compared young adults destined to develop asthma with control subjects to determine differences between them before diagnosis.

Methods: Subjects were participants of the Tucson Epidemiologic Study of Airways Obstructive Disease. They were studied between the ages of 15 and 19 and subsequently every 1 to 2 years until they were at least 21 years old with questionnaires, spirometry, allergy skin testing, and serum IgE testing.

Results: Logistic regression showed that "wheeze" and "attacks of shortness of breath with wheeze" were independently predictive of asthma. Positive allergy skin test results occurred more frequently among subjects who later received a diagnosis of asthma, and initially these subjects had higher serum IgE levels than control subjects (geometric mean IgE = 173.8 IU/ml vs 52.5 IU/ml for control subjects; $p < 0.005$). Although initial spirometric testing did not distinguish between future asthmatic subjects and control subjects, repeat testing after diagnosis did show significant differences in flows at low lung volumes.

Conclusions: These data suggest that symptoms and findings suggestive of asthma may be present for many years before diagnosis. (*J ALLERGY CLIN IMMUNOL* 1994;94:831-5.)

Key words: Asthma, adults, allergy, incidence, serum IgE

In the last 30 years, large-scale community studies have provided basic information about the epidemiology of asthma.¹⁻⁴ In these reports the prevalence and incidence of the disease, as well as the course after diagnosis, are well-described, particularly in children. Also, in attempts to determine who in the general population is predisposed to the development of asthma, investigators have compared asthmatic individuals with control subjects. These comparisons have shown that asthmatic children are more likely to be atopic and to have a history of respiratory infections

Abbreviations used

ANOVA:	Analysis of variance
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
NDA:	New diagnosis of asthma
SOBWZ:	Shortness of breath with wheezing
Vmax 50%:	Maximum expiratory flow at 50% of the FVC

than are healthy children.⁵ Because such correlations have been found after the diagnosis of asthma has been made, however, they do not clearly establish risk factors for the disease.

Among adults, even less is known about differences between asthmatic individuals and others because few longitudinal data are available in persons over age 21. Among elderly asthmatic subjects (over age 60) of the Tucson Epidemiologic Study of Airways Obstructive Diseases,⁶ we reported that asthma-like symptoms were present

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for many years before a diagnosis was made, so that subjects with symptoms such as wheezing were at increased risk of receiving a diagnosis of asthma. In addition, evidence of allergy, such as allergy skin test reactivity and relatively high serum IgE levels, was more common before the diagnosis of asthma in elderly subjects, suggesting that as in younger subjects, evidence of allergy is a risk factor for the disease in older persons.

In the Tucson study we have also studied children prospectively. We recently compared young subjects who subsequently received a diagnosis of asthma with control subjects,⁷ and we found that wheezing and other respiratory symptoms, as well as markers of allergy, often preceded the diagnosis of asthma and increased the risk for the disease. In addition, the data revealed that longstanding symptoms rather than a precipitating event characterized the natural history of asthma before diagnosis.

We now report on young adults, an age group in which we and other researchers have found a low incidence of asthma. In a study of residents of Rochester, Minnesota, investigators found the lowest incidence of asthma among subjects 15 to 50 years of age.² As we previously reported, the incidence of asthma among Tucson subjects falls sharply after age 10 and does not increase significantly again until after age 60.³

After 12 surveys and nearly 20 years of observation, we have accumulated 29 cases of new asthma first diagnosed when the subjects were between the ages of 20 and 39. In this article we compare these subjects to control subjects both before and after diagnosis in order to describe more fully the disease in this age group.

METHODS

Subjects are participants in the Tucson Epidemiologic Study of Airways Obstructive Diseases, a longitudinal study of a representative sample of white, non-Mexican-American households in Tucson, Arizona. Methods of selection of the overall population sample have been reported in detail.⁸ Briefly, the sample consists of a random cluster sample of households in the city from 1971 to 1972, stratified on the basis of age of head of household and socioeconomic status. Over the years, we have continued to enroll new members of these households, primarily new spouses and newborns.

For this study, we have selected those subjects who answered questionnaires when they were 15 to 19 years of age (the baseline period) and who had follow-up evaluations until they were at least 21 years of age. When more than one questionnaire was answered between ages 15 and 19, the earliest was used for baseline data. Subjects who claimed a history of asthma

(whether or not it was confirmed by a physician) on their baseline questionnaire were excluded from the study, as were two subjects who received a diagnosis of asthma between the ages of 15 and 19.

There were 467 subjects who met our inclusion criteria, and 29 of them had a new diagnosis of asthma (NDA) between the ages of 20 and 39. The remaining 438 subjects were considered control subjects. The mean ages at baseline evaluation were 16.6 years for NDA subjects and 16.7 years for control subjects. Thus the number of years at risk was 11.2 for the NDA group and 9.5 for the control group. None of these differences in ages or number of years at risk reached statistical significance.

In most follow-up surveys, NDA was determined by a "yes" response to the question: "During the past year, have you seen a doctor for asthma?" In some of the later surveys, the subjects were asked: "Have you ever had asthma?" We considered NDA to be present only if subjects also answered "yes" to the subsequent question: "During the past year, have you seen a doctor for it?" We also derived the rates of respiratory complaints from questionnaire responses. For example, we considered a subject to have a cough if there was a "yes" response to "Do you usually cough in bad weather?" or "Do you ever have a cough when you don't have a cold?"

Methods of spirometric testing, allergy skin testing, and serum IgE measurements have been reported.⁹⁻¹¹ Not all subjects had complete testing because some moved away from Tucson before their baseline period (15 to 19 years of age) or in subsequent years. In addition, allergy skin tests and serum IgE measurements were not done at each evaluation, and some subjects living in Tucson may have missed these tests while they were between the ages of 15 and 19. To maximize the data, we have included allergy skin test results and serum IgE measurements from these subjects obtained between the ages of 10 and 19 if data were not available from the time that they were between the ages of 15 and 19. Skin test results (any reaction greater than the control diluent test was considered positive) were available for 396 subjects, and IgE levels were available for 289 subjects. The mean ages of NDA subjects and control subjects at the time of allergy skin testing (15.4 vs 15.0 years) and at the time of serum IgE measurements (15.6 vs 15.7 years) were not significantly different.

Serum IgE levels have a logarithmic distribution and vary according to age and sex.¹⁰ We report them here as age-sex-standardized Z scores, the score being the number of standard deviations by which a subject's log IgE level differed from the mean log IgE for his or her age-sex-specific group.

Baseline spirometric results are reported only for tests done in subjects between 15 and 19 years of age. We obtained satisfactory spirograms for 367 subjects. We also report the spirometric results in 355 subjects who had testing done after age 20, at an average age of

TABLE 1. Findings at baseline in subjects with NDA and control subjects

	Group		<i>p</i> Value	RR ± (95% CI)*
	NDA	Control		
No. of subjects	29	433		
% Male	48.3	47.3	NS	1.0 (0.69-1.5)
Percent with				
Wheezing	58.6	19.2	<0.0001	5.1 (2.5-10.4)
SOBWZ	31.0	6.0	<0.0001	5.5 (2.7-11.1)
Cough or sputum production	27.6	18.9	NS	1.6 (0.72-3.4)
Rhinitis	69.0	38.6	<0.005	3.3 (1.5-7.0)
Any wheeze or SOBWZ	69.0	20.4	<0.0001	7.2 (3.4-15.4)
Severe chest infection	48.3	29.9	0.06	2.1 (1.0-4.2)
History of smoking (ever)	58.6	49.8	NS	1.2 (0.85-1.6)
History of chronic bronchitis	10.3	7.3	NS	1.4 (0.46-4.3)
Positive skin test results (N)	68.3 (25)	41.2 (371)	<0.02	2.8 (1.2-6.4)

RR, Relative risk; CI, confidence interval; NS, not statistically significant.

*Relative risk of NDA in those with the finding compared with those without the finding.

†Severe enough to interfere with the subject's "usual activities."

28.6 years. Reference equations for determining percent predicted values for the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and the maximum expiratory flow at 50% of the FVC (Vmax50%) were derived from findings in asymptomatic nonsmokers in the population.¹¹ All aspects of the research have been reviewed and approved by the University of Arizona Human Subjects Committee.

Statistical methods included simple and trend chi square analysis, relative risk ratios, analysis of variance (ANOVA), and multiple logistic regressions. Findings were considered statistically significant if their likelihood of occurrence by chance was less than 0.05. All reported *p* values are two-tailed.

RESULTS

Of the 467 studied subjects, 6.2%, 15 female and 14 male subjects received a new diagnosis of asthma. The average age of the subjects at the time of reporting asthma was 27.6 years, and the average time between baseline examination and a report of NDA was 11.0 years. We have calculated the annual incidence rate of asthma diagnoses in our subjects as 0.65%, with the rate slightly higher in male subjects.

In Table 1 we compare the subjects with NDA with control subjects at their evaluations before age 20. Wheezing, attacks of shortness of breath with wheeze (SOBWZ), and rhinitis were all significantly more frequent at baseline in subjects who developed NDA (*p* < 0.05 by chi square analysis). Either wheeze or SOBWZ or both occurred in 69% of subjects with NDA before diag-

nosis and in only 20% of the control subjects. There were no significant differences between the NDA group and the control group in the frequency of chronic cough or production of sputum, the frequency of a history of smoking, or in the frequency of a diagnosis of chronic bronchitis.

The initial symptoms of many of the subjects with NDA worsened over time. Among the 20 subjects with wheezing before diagnosis, for example, seven reported wheezing "only with colds." After diagnosis, all seven reported wheezing "even apart from colds." Such a progression of symptoms did not occur in the control subjects. Of the 83 control subjects with wheezing at baseline, 44 reported the complaint "only with colds," and of these, only 10 reported wheezing "even apart from colds" in a subsequent evaluation.

To determine whether symptoms before a diagnosis of asthma primarily predicted NDA that occurred shortly after the baseline period, a finding that would suggest that the symptoms were simply undiagnosed disease, we repeated the above analyses on the NDA group whose diagnoses were made after age 28. The mean age of reported NDA in these 10 subjects was 33.2 years, an average of 16.3 years after the baseline period. Even in this group, wheeze and SOBWZ were significant predictors of NDA. One or both of these symptoms had been present in eight of the 10 subjects at baseline, compared with a rate of 20.4% in control subjects (*p* < 0.001 by chi square analysis).

TABLE II. Mean of pulmonary function test results ($\pm$ SD) in subjects with NDA and control subjects

	Group		<i>p</i> Value*
	NDA	Control	
Results obtained during baseline (ages 15-19)			
No. of subjects	25	342	
% Predicted FVC	103.7 ± 11.3	103.8 ± 13.1	NS
% Predicted FEV ₁	102.2 ± 10.4	102.5 ± 13.1	NS
FEV ₁ /FVC (%)	86.8 ± 5.5	86.9 ± 7.2	NS
% Predicted Vmax 50%	93.8 ± 19.9	99.7 ± 23.8	NS
Results obtained after age 20			
No. of subjects	24	331	
% Predicted FVC	105.8 ± 10.9	107.2 ± 12.8	NS
% Predicted FEV ₁	100.1 ± 11.3	104.2 ± 12.6	NS
FEV ₁ /FVC (%)	80.1 ± 5.9	82.7 ± 6.5	0.06
% Predicted Vmax 50%	86.7 ± 22.0	97.4 ± 23.9	<0.05

NS, Not statistically significant.

**p* values were determined by ANOVA.

Stepwise logistic regression results showed that both wheeze and SOBWZ were independently predictive of NDA. No other variable listed in Table I entered the regression at a significant level. Similarly, when "wheeze and/or SOBWZ" was entered as a single variable, no other variable in Table I contributed significantly to the regression.

As expected, subjects with NDA had more indicators of allergy than control subjects before diagnosis. As shown in Table I, subjects with NDA had a significantly higher rate of positive allergy skin test results than control subjects. The geometric mean IgE level for the NDA group (18 subjects were tested) was 173.8 IU/ml compared with 52.5 IU/ml in the 271 control subjects ($p < 0.005$ by ANOVA). When expressed as Z scores, serum IgE levels were 0.701 ± 0.60 in the NDA group and -0.302 ± 0.00 in the control group ($p < 0.005$ by ANOVA). Of note, no subject with NDA had an actual IgE level less than 44 IU/ml between the ages of 10 and 19, whereas over 40% of control subjects had values below this level.

Spirometric data are presented in Table II. As shown, no significant differences were seen between subjects with NDA and control subjects at baseline, although percent predicted Vmax50% showed a trend toward lower values in the subjects with NDA. When the subjects were retested after the age of 20 (the average age at retesting was 28.6 years), the NDA group had a significantly lower Vmax50%, with a trend toward lower values of percent predicted FEV₁ and FVC as well.

DISCUSSION

In this report we have described 29 young adults who received an NDA during almost 20 years of observation. The annual incidence of 0.65% among our subjects between the ages of 20 and 39 is slightly higher than the rate we reported for this age group after approximately 4 years of observation³ and slightly lower than the rate we reported in adults after 12 years,¹² but the small number of cases does not allow us to conclude that asthma is becoming more common in young adults.

As shown in Table I, many of the subjects with NDA had symptoms suggesting a mild "subclinical" asthmatic state before diagnosis. The 10 subjects with NDA who were diagnosed after age 28 had wheezing for an average of 16 years before they were diagnosed as having asthma. In addition, as the data on the progression of wheezing in our subjects suggests, subjects with NDA had gradually worsening symptoms until they were finally declared asthmatic by their physicians. We have found similar precursory symptoms in other age groups that we have studied and believe that it is an important aspect of the natural history of asthma.⁷

How often these subjects consulted physicians before diagnosis is unknown to us. Unlike other age groups that we have studied, they have not received other diagnostic labels, such as chronic bronchitis, any more frequently than control subjects. In contrast, among subjects with NDA first diagnosed between the ages of 10 and 19, roughly one third had been diagnosed with chronic bron-

chitis before asthma developed.⁷ Among the elderly, almost one half of the subjects with NDA had a diagnosis of chronic bronchitis either before or at the time that they were diagnosed as having asthma. As we have speculated previously, the use of other diagnostic labels in subjects in whom asthma eventually develops may reflect the reluctance of physicians to use the term "asthma," with its implication of chronic illness⁷; or, for example, in the case of elderly men with a history of wheezing and smoking cigarettes, physicians may not consider "asthma" an appropriate diagnosis.⁵

Our results also show that indicators of allergy helped distinguish our subjects with NDA from control subjects. Both the rate of positive allergy skin test results and the geometric mean IgE level (or log serum IgE level) were much higher in subjects with NDA than in control subjects. Unfortunately, even among subjects in a relatively narrow age range, serum IgE levels do not permit a clinician to determine which patients with wheezing are most likely to have persistent symptoms and eventually be diagnosed as having asthma. We do believe, however, that because none of the subjects with NDA had serum IgE values below the mean (adjusted for age and sex), a value below normal in a young adult with mild or brief wheezing should discourage the diagnosis of asthma.

Pulmonary function tests were of little use in separating subjects with NDA from control subjects before diagnosis. Functional abnormalities compatible with mild airway obstruction were noted after diagnosis, indicating that pulmonary function did not continue to develop normally in those subjects with NDA. As noted by Woolcock et al.,¹³ the Vmax50% appears to be a more sensitive indicator of disease than other spirometric measurements in young asthmatic subjects.

When compared with other age groups with NDA, our group had spirometric test results similar to those found in children.⁷ That is, baseline testing produced no significant differences between children destined to develop asthma and control subjects, but later testing did produce differences.

The finding most deserving of emphasis in this study is that many of our subjects had mild symptoms suggestive of asthma for many years before diagnosis and thus the actual time of onset of the disease was impossible to determine. In our clinical practice we have found that new adult asthmatic patients do not typically give a history

of years of wheezing or other symptoms, but rather they report a precipitating event, such as a severe respiratory infection, as the beginning of their illness. Only through the long-term prospective study of a general population sample have we learned to appreciate the long prodrome and slowly progressive nature of asthma. Consequently, we suspect that many patients who are first seen with a history of short duration of illness have had mild symptoms for many years, which they do not recall.

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