

CHEST[®]

Official publication of the American College of Chest Physicians



Asthma Features in Severe α_1 -Antitrypsin Deficiency^{*}

Edward Eden, Jeffrey Hammel, Farshid N. Rouhani, Mark L. Brantly, Alan F. Barker, A. Sonia Buist, Robert J. Fallat, James K. Stoller, Ronald G. Crystal and Gerard M. Turino

Chest 2003;123:765-771
DOI 10.1378/chest.123.3.765

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://www.chestjournal.org/content/123/3/765.full.html>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.
(<http://www.chestjournal.org/site/misc/reprints.xhtml>) ISSN:0012-3692

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Asthma Features in Severe α_1 -Antitrypsin Deficiency*

Experience of the National Heart, Lung, and Blood Institute Registry

Edward Eden, MD; Jeffrey Hammel, PhD; Farshid N. Rouhani, PhD;
Mark L. Brantly, MD; Alan F. Barker, MD, FCCP; A. Sonia Buist, MD;
Robert J. Fallat, MD; James K. Stoller, MD, FCCP; Ronald G. Crystal, MD; and
Gerard M. Turino, MD; and the α_1 -Antitrypsin Deficiency Registry Study Group

Study objectives: To describe asthma features in a cohort with α_1 -antitrypsin (AAT) deficiency, and determine the impact of asthma on FEV₁ decline.

Background: Asthma may be common in those with AAT deficiency, and may lead to accelerated airflow obstruction.

Design: Analysis of data obtained from a 5-year, prospective National Heart, Lung, and Blood Institute registry.

Setting: A multicenter registry consisting of 37 clinical centers, a central phenotyping laboratory, and a data analysis center.

Participants: A cohort of 1,052 subjects with AAT deficiency.

Measurements and results: Asthma was defined as reversible airflow obstruction, recurrent attacks of wheezing, and a reported diagnosis of asthma or allergy with or without an elevated serum IgE level. FEV₁ decline was calculated by least-square means with adjustments for covariables. Asthma was present in 21% of the cohort and in 12.5% of those with a normal FEV₁. Attacks of wheezing were reported in 66%, the first attack occurring at a mean \pm SD age of 31 \pm 16 years. Allergy and asthma was reported in 29% and 38%, respectively. An elevated IgE level occurred in 17% and was significantly associated with signs and symptoms of asthma and an allergy history. Unadjusted FEV₁ decline was less in the group without asthma and a normal IgE level (-48.5 mL/yr) vs the groups with asthma features (≥ 64 mL/yr) [$p = 0.002$]. Multivariable analysis showed that bronchodilator response, age, and smoking were significant predictors for FEV₁ decline but not asthma.

Conclusions: Symptoms and signs of asthma are common in AAT deficiency and may start at the age of most rapid FEV₁ loss. Adjusting for other risk factors such as bronchodilator response, asthma as defined does not lead to an accelerated FEV₁ decline. In AAT deficiency, augmentation therapy is not more effective in preventing the loss of lung function in those with asthma compared to those without. (CHEST 2003; 123:765-771)

Key words: α_1 -antitrypsin deficiency; asthma; lung disease, obstructive

Abbreviations: AAT = α_1 -antitrypsin; NHLBI = National Heart, Lung, and Blood Institute

Previous reports indicate that in α_1 -antitrypsin (AAT) deficiency symptoms and signs of asthma occur with emphysema.¹⁻⁴ The diagnosis of asthma

is difficult because the major characteristics of asthma, episodic wheezing and reversible airway obstruction, are common in populations with a diag-

*From the James P. Mara Center for Lung Disease (Drs. Eden and Turino), St Luke's-Roosevelt Hospital Center, New York, NY; Cognigen Corporation (Dr. Hammel), Buffalo, NY; National Institutes of Health (Dr. Rouhani), Bethesda, MD; University of Florida College of Medicine (Dr. Brantly), Gainesville, FL; Oregon Health Sciences University (Drs. Barker and Buist), Portland, OR; California Pacific Medical Center (Dr. Fallat), San Francisco, CA; Cleveland Clinic Foundation (Dr. Stoller), Cleveland, OH; and New York Hospital-Cornell Medical Center (Dr. Crystal), New York, NY.

Supported by National Heart, Lung, and Blood Institute contract No. NO1-HR-86036.

Manuscript received February 6, 2002; revision accepted August 5, 2002.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Edward Eden, MD, James P. Mara Center for Lung Disease, St Luke's-Roosevelt Hospital Center, Room 3A-55, 1000 10th Ave, New York, NY 10019; e-mail: eeden@chpnet.org

nosis of COPD.^{5,6} These clinical features may be related to anatomy of the small airways and loss of elastic recoil rather than those immune-mediated inflammatory processes commonly found in patients with asthma.⁷

Although smoking is the most important risk factor for development of early emphysema in those with severe AAT deficiency, it may not be the only factor contributing to the development of airflow obstruction. For example, the National Heart, Lung, and Blood Institute (NHLBI)-sponsored AAT registry reported that a bronchodilator response is one factor that is associated with a more rapid decline in FEV₁.⁸ The impact of asthma on the course of irreversible airflow obstruction in those with severe AAT deficiency is poorly understood. Lack of an effective airway antiprotease screen may increase the propensity to inflammation, which may lead to airway remodeling and an accelerated FEV₁ decline. It was therefore determined if a greater FEV₁ decline occurred in registry participants showing the clinical features of asthma compared to those without.

If such a decline is in part caused by the lack of an effective antiprotease screen in the lower airways, increasing the airway concentration of AAT by augmentation therapy might ameliorate inflammation, reduce airway responsiveness, and preserve airway integrity. Therefore, we also examined whether augmentation therapy with AAT reduced the rate of FEV₁ decline in the group with features of asthma.

MATERIALS AND METHODS

The organizational structure of the NHLBI-sponsored registry has been described previously.⁹ The study was designed to prospectively study, over 5 years, the natural history of a cohort of subjects with AAT deficiency. The total number of participants enrolled was 1,129. All participants were \geq 18 years old, provided informed consent, and had a serum AAT level $<$ 11 μ mol/L (or genotypic P1^{ZZ} by DNA probe analysis) as determined by a central laboratory. At each visit, spirometry measurements were obtained before and after bronchodilator according to American Thoracic Society criteria. Highly reproducible measurements were achieved.¹⁰ A single IgE determination was made on stored serum collected during the first visit using antigenic nephelometry (Behring Diagnostics; Westwood, MA) and a commercial standard (Behring Diagnostics).

All participants completed the American Thoracic Society-Division of Lung Disease 1978 questionnaire⁹ on the initial visit, and modified forms were completed on subsequent visits. The responses to question 13 (Does your chest ever sound wheezy or whistling?) and question 14 (Have you ever had an attack of wheezing that has made you feel short of breath?) and responses to questions of previous doctor-diagnosed asthma and respiratory allergies were analyzed. Participants were defined as having asthmatic features if they had the following: (1) demonstrated a \geq 12% improvement in FEV₁ of at least 200 mL after bronchodilator on any visit, (2) had a history of more than one attack of wheezing with shortness of breath, and (3) reported a doctor's diagnosis of asthma or allergy. Those fulfilling this definition

were further subdivided according to the serum IgE concentration. This definition is based on an earlier work by the authors.³

The use of augmentation therapy refers to the IV infusion of purified AAT at a weekly dose of 60 mg/kg. The decision to use this therapy, the dose, and schedule was determined by the subjects' personal physician. For the purposes of this study, subjects were classified as having ever or never received augmentation therapy during the study.

Analysis of Data

Categorical data were summarized as frequencies and percentages, and quantitative data were summarized by the mean and either SD or SE. Serum IgE concentrations in international units per milliliter from 61% of the participants were reported as $<$ 33.1. IgE concentrations were grouped as high (\geq 100 IU/mL) and low ($<$ 100 IU/mL).¹¹ Comparisons of the IgE groups were performed by χ^2 tests for categorical data. Spearman rank correlation coefficients described the association between the ordinal IgE categories and continuous variables. Reported *p* values are considered statistically significant if \leq 0.05.

As previously described,⁸ the FEV₁ slope for individuals was calculated for those with two or more postbronchodilator measurements obtained \geq 1 year apart. Using a linear mixed-effects model,¹² a least-squares regression of FEV₁ vs time since enrollment was calculated. Analysis of variance was used to analyze the mean FEV₁ decline with respect to the interaction between asthma and an elevated IgE, and between asthma and augmentation therapy for all subjects. These analyses were also performed with adjustments for gender, smoking status, age, and bronchodilator response. Least-squares means were computed to provide estimates of mean FEV₁ decline for subgroups of patients.

RESULTS

Prevalence of Asthma Features in the Cohort

This report is based on 1,052 of 1,129 participants (93%) who completed questionnaires, spirometry, and for whom IgE data were available. Of this cohort, 56% are of male gender, with a mean \pm SD age of 46 ± 11 years and mean FEV₁ of $47 \pm 30\%$ predicted. The mean serum AAT level for the cohort is 5.8 ± 1.4 μ mol/L.

Of the 1,052 participants, 82% reported wheezing without a cold, almost 90% of subjects reported wheezing with a cold, and 66% reported more than one wheezing attack with shortness of breath (Table 1). Of those with wheezing attacks, 62% required medication. The mean \pm SD age of onset of the first attack was 31 ± 16 years. Self-reported respiratory allergy and asthma diagnosed by a doctor occurred in 29% and 38%, respectively.

A significant bronchodilator response occurred in 28% of individuals during the first visit and in 49% over all visits (mean number of visits, 5.0 ± 2.5). In those with a significant bronchodilator response, the mean value of the maximum FEV₁ increase over all visits was 382 ± 180 mL (median, 330 mL; range, 202 to 1,492 mL). Based on the percentage of

Table 1—Occurrence of Wheezing Variables, Allergy, and Asthma*

Variables	% With Feature at Baseline (n = 1,052)	% With Feature on Follow-up (n = 939)	% With Feature at Any Visit (n = 1,052)
Wheeze with cold	75.7 (n = 1,049)	87.3	89.6
Wheeze without cold	65.7	79.6	82.3
Wheeze most days or nights	33.4 (n = 1,051)	51.5	55.3
Wheezing "attacks" with shortness of breath > 1 episode	50.5	66.0	69.3
Required medication	46.5	63.3	66.1
Age at first attack, yr	42.3	59.4	62.3
	33.8 ± 14.6 (n = 521)	31.4 ± 16.1 (n = 615)	31.1 ± 16.1 (n = 724)
Self-reported allergy	28.5	1.8	29.2
Self-reported asthma	34.7	6.9	37.5

*Data are presented as No. or mean ± SD.

predicted, the mean increase was $37.6 \pm 23.1\%$ (median, 33.3%; range, 12 to 316%).

Asthma Features in the Cohort

The percentage of subjects showing asthma features at any visit according to the presence of significant airflow obstruction is shown in Table 2. Clinical features of asthma are present in 21% overall, in 23% (197 of 857 patients) with significant airflow obstruction ($FEV_1 < 80\%$) and in 12.5% (23 of 184 patients) with an FEV_1 of $\geq 80\%$. A much smaller proportion of the cohort with asthma have an elevated IgE, approximately 5% in the group with airflow obstruction (43 of 857 patients) and 7% in the group without (13 of 184 patients). As expected, the mean maximum improvement in FEV_1 after bronchodilator is greater in the groups with asthma compared to the groups without (372 ± 189 mL vs 214 ± 156 mL, $p < 0.001$; and 459 ± 221 mL vs 228 ± 226 mL, $p < 0.001$, for the groups with normal and elevated IgE levels, respectively).

Relationship of Elevated Serum IgE Level to Asthma-Associated Symptoms and Signs

The relationship of key variables to the presence or absence of an elevated IgE level was determined

(Table 3). An IgE level ≥ 100 IU/mL, present in 176 of the cohort (16.7%), is significantly more common in male subjects and significantly associated with some wheezing variables or a history of asthma or allergy. An elevated IgE level (≥ 100 IU/mL) is neither associated with a smoking history nor with attacks of shortness of breath.

There is a slight but significant correlation between maximum FEV_1 bronchodilator response for all visits and the IgE level ($r = 0.12$, $p < 0.001$). This relationship is not observed when FEV_1 is expressed as the percentage of predicted.

Maximum FEV_1 in the Groups Showing Asthma Features

A comparison of the maximum postbronchodilator FEV_1 (percentage of predicted \pm SE) at any visit was made according to the presence of asthma and an elevated IgE level. In the presence of a normal IgE level, the group with asthma has a significantly lower FEV_1 percentage of predicted than the group without clinical asthma ($41 \pm 1.6\%$ vs $48 \pm 1.3\%$, analysis of variance $p = 0.005$). In the presence of an elevated IgE level, there is no significant difference in FEV_1 percentage of predicted in the group with clinical features of asthma compared to the group without ($51 \pm 4.5\%$ vs $48 \pm 1.3\%$, $p = 0.1$).

Table 2—Prevalence of Asthma in the Cohort According to the Presence of Airflow Obstruction and an Elevated IgE*

Variables	Bronchodilator Response at Any Visit, and > 1 Wheezing Attack, and Allergy or Asthma at Any Visit		Bronchodilator Response at Any Visit, and > 1 Wheezing Attack, and Allergy or Asthma at Any Visit, and IgE ≥ 100 IU/mL	
	Yes	No	Yes	No
Airflow obstruction (n = 857)	197	660	43	814
No airflow obstruction (n = 184)	23	161	13	171
Totals	220 (21.1)	821 (78.9)	56 (5.4)	985 (94.6)

*Data are presented as No. or No. (%).

Table 3—Relationship of Key Variables to an Elevated IgE*

Variables	IgE Level, IU/mL		p Value
	< 100 (n = 876)	≥ 100 (n = 176)	
Serum AAT level	5.76 ± 1.38 (n = 796)	5.80 ± 1.42 (n = 163)	0.65
Male gender, %	52.5	72.7	< 0.001
Bronchodilator response ever	47.8 (n = 862)	54.5	0.10
Wheeze a lot ever	53.8	63.1	0.024
Attacks with shortness of breath ever	69.2	69.9	0.85
Asthma ever	36.2	44.3	0.042
Allergy ever	26.7	41.5	< 0.001
Smoked at all ever	80.3 (n = 856)	78.8 (n = 170)	0.67

*Data are presented as mean ± SD or No. unless otherwise indicated.

Rate of FEV₁ Decline in the Groups Showing Asthma Features

Median follow-up for the cohort was 52 months (range, 12 to 86 months). Table 4 shows statistically significant differences in mean rates of FEV₁ decline by gender, smoking status, age, and bronchodilator response, as well as the presence of asthma features. The presence of significant airflow obstruction just fails to reach significance as a predictor of FEV₁ decline in this model (p = 0.06).

The mean rate of decline in FEV₁ is lower for the group without asthma features or an elevated IgE level. The difference is significant when this group was compared to the group with asthma (− 70 mL/yr vs − 48.5 mL/yr, p = 0.004). Interestingly, the group without asthma but an elevated IgE level also shows a significantly higher rate of FEV₁ decline when compared with the normal IgE level no-asthma group (− 74.9 vs − 48.5 mL/yr, p = 0.005).

Multivariable Analysis of FEV₁ Decline According to the Presence of Asthma Features and Airflow Obstruction

Gender, smoking status, age, and bronchodilator response are included as covariables in a multivariable model to describe the relationships between asthma and airflow obstruction on the mean rate of FEV₁ decline (Table 5). After adjusting for these covariables, age, smoking status, and bronchodilator response are significant independent predictors for FEV₁ decline in this model (p < 0.001). The most rapid decline in FEV₁ occurs in the age group (30 to 44 years) that coincides with the mean age of onset of self-reported wheezing (31 ± 16 years). Asthma as defined is not a significant predictor (p = 0.09).

Table 4—Univariable Analysis of FEV₁ Decline in Milliliters per Year

Variables	Least-Squares Mean	95% Confidence Interval	p Value
Gender			
Male	− 64.3	(− 71.6 to − 57.0)	0.001
Female	− 45.5	(− 53.7 to − 37.3)	
Smoking status			
Never	− 54.5	(− 66.3 to − 42.8)	0.041
Ex-smoker	− 53.7	(− 60.2 to − 47.1)	
Current	− 79.8	(− 99.0 to − 60.5)	
Age, yr			
< 30	− 43.4	(− 67.6 to − 19.3)	0.002
30–44	− 73.3	(− 83.4 to − 63.2)	
45–54	− 48.7	(− 57.8 to − 39.7)	
55–64	− 54.3	(− 66.7 to − 41.9)	
≥ 65	− 41.5	(− 58.7 to − 24.4)	
Bronchodilator response			
Ever	− 69.0	(− 76.3 to − 61.7)	< 0.001
Never	− 39.9	(− 48.0 to − 31.8)	
Airflow obstruction			
Yes	− 58.5	(− 64.6 to − 52.4)	0.06
No	− 45.3	(− 57.9 to − 32.7)	
Asthma, IgE			
Asthma, high IgE	− 64.0	(− 85.8 to − 42.2)	0.002
Asthma, normal IgE	− 70.0	(− 83.1 to − 57.0)	
No asthma, high IgE	− 74.9	(− 91.9 to − 57.9)	
No asthma, normal IgE	− 48.5	(− 55.2 to − 41.8)	

Effect of Augmentation Therapy on FEV₁ Decline According to the Presence of Asthma Features

By extending the multivariable model to include the use of augmentation therapy, the effect of augmentation therapy on FEV₁ decline according to the presence or absence of asthma was determined. There is no significant difference in either the number of follow-up visits (mean range, 4.8 to 6.4 visits; median range, 5 to 6 visits) or the follow-up time (mean range, 47 to 60 months; median range, 48 to 60 months) between those ever and never receiving augmentation therapy for each group. The percentage of subjects receiving augmentation therapy ranges from 67 to 82% for the asthma/IgE groups defined in Tables 4, 5.

Smoking status, age, and bronchodilator response remain significant predictors of FEV₁ decline. In the group with asthma and an elevated IgE level (n = 36), FEV₁ decline is significantly less in those not receiving augmentation compared to the group receiving this therapy (n = 18) [p = 0.043]. There was no effect of augmentation therapy on FEV₁ decline in the other groups when compared by asthma features.

The mean baseline FEV₁ percentage of predicted for the subgroups not receiving augmentation therapy was significantly greater than for those receiving

Table 5—Multivariable Analysis of FEV₁ Decline in Milliliters per Year

Variables	Least-Squares Mean	95% Confidence Interval	p Value
Gender			
Male	-59.7	(-67.0 to -52.3)	0.16
Female	-51.3	(-59.7 to -43.0)	
Smoking status			
Never	-64.3	(-77.3 to -51.4)	0.048
Ex-smoker	-51.4	(-58.0 to -44.8)	
Current	-73.0	(-92.5 to -53.6)	
Age, yr			
< 30	-43.9	(-68.9 to -18.8)	0.004
30-44	-72.5	(-82.8 to -62.3)	
45-54	-48.9	(-58.0 to -39.9)	
55-64	-54.4	(-66.9 to -42.0)	
≥ 65	-42.4	(-60.1 to -24.7)	
Bronchodilator response			
Ever	-68.0	(-76.0 to -60.0)	< 0.001
Never	-41.1	(-50.2 to -32.0)	
Airflow obstruction			
Yes	-58.2	(-64.4 to -52.0)	0.17
No	-46.5	(-61.1 to -32.0)	
Asthma, IgE			
Asthma, high IgE	-47.9	(-70.2 to -25.5)	0.09
Asthma, normal IgE	-54.7	(-68.7 to -40.6)	
No asthma, high IgE	-76.2	(-93.1 to -59.3)	
No asthma, normal IgE	-53.9	(-60.7 to -47.1)	

therapy (*t* test *p* < 0.001). However, there was no evidence of an interaction between baseline FEV₁ percentage of predicted and augmentation therapy in this model (*p* = 0.36).

DISCUSSION

This study describes the features of asthma in a large cohort of subjects with severe AAT deficiency. It shows that a high proportion of subjects report wheezing symptoms and show a bronchodilator response. Wheezing is reported in > 80% at baseline and almost universally during a respiratory infection. Nearly 70% of participants report attacks of wheezing with shortness of breath. This study also shows that the first attack of wheezing was self-reported to occur at a mean age of 31 years, a decade and a half before the mean age of presentation to the AAT registry. It is unknown whether this symptom results from early development of emphysema, an asthmatic condition, or both. It is possible that a condition diagnosed by physicians as asthma develops as an early manifestation in those destined to acquire emphysema.

A purpose of this study is to determine if asthma is associated with AAT deficiency. The diagnosis of asthma in any group with COPD is difficult because

wheezing and reversible airflow obstruction are common manifestations of both conditions. For example, the Intermittent Positive Pressure Breathing trial⁵ of 985 subjects reported a mean wheezing score of approximately 2, meaning occasionally with exercise and an average bronchodilator response of 15% baseline. The Lung Health Study,¹³ which enrolled subjects with mild airflow obstruction (mean FEV₁, 75.1 ± 8.8%), reported a bronchodilator response of ≥ 10% baseline in 10.9% of participants and physician-confirmed asthma from 6.8 to 7.6%. In the Tucson study, Sherrill et al¹⁴ described self-reported asthma in approximately 17% of cigarette smokers aged 35 to 55 years and in approximately 13% of nonsmokers aged > 35 years.

Wheezing in chronic airflow obstruction is likely to result in part from a reduction of airway diameter due to loss of elastic recoil. Indeed, bronchodilator response as a percent of FEV₁ becomes more common the lower the baseline FEV₁.⁵ In the current study, a bronchodilator response occurred in nearly half of subjects and in 12.5% of those with a normal FEV₁ (*n* = 184). This percentage is greater than has been reported in general population studies. In 2,609 healthy subjects, Dales et al¹⁵ reported that the 95th percentile of bronchodilator response was 9% and occurred in approximately 3% of those with a normal FEV₁. Lorber et al¹⁶ reported 10% of a cohort of 1,063 subjects exceeded a change in FEV₁ of 7.7% after bronchodilator. However, of this group, 65 subjects were asthmatics. The increased percentage of subjects with a normal FEV₁ showing a response to bronchodilator suggests that bronchial hyperresponsiveness and asthma may occur at an early stage of the natural history of lung disease in AAT deficiency.

Previous studies indicate that clinical features of asthma are present in a proportion of those with severe AAT deficiency. A diagnosis of asthma was considered present in 11% of 166 patients with PI*Z AAT deficiency participating in a British Thoracic Society survey.⁴ More recently, Piitulainen et al¹⁷ reported a mean bronchodilator response of 400 mL (6%) in 41% of a group of 225 never-smoking subjects with severe AAT deficiency. The mean FEV₁ for the cohort was 2.4 L (84% predicted), with only 13 of the group showing a postbronchodilator rise in FEV₁ > 15%. In another case series of 52 subjects with AAT deficiency, self-reported asthma was present in 25% of those with an FEV₁ < 65% predicted.¹⁸ Wheezing was present in 60% of this group. In the current study, using a definition similar to that previously reported,³ asthma was present in 21% of this large cohort.

Eden et al³ used total serum IgE level and atopy to refine the definition of asthma in a group with severe

AAT deficiency. Although the number of subjects was small in this study, asthma associated with atopy was more common in subjects with emphysema and severe AAT deficiency than in those with COPD without the deficiency. In the current study total serum IgE level was used as a surrogate marker for atopy that is known to be associated with bronchial hyperresponsiveness.^{11,19} An elevated total serum IgE level (≥ 100 IU/mL) is found in nearly 17% of this cohort and is more common in men, in those with self-reported allergy and asthma, a history of wheezing, and in subjects showing a bronchodilator response. There is also a weak but statistically significant correlation between total IgE and absolute maximum FEV₁ bronchodilator response. Thus, an elevated IgE is a marker for a history of atopy, and defines in our cohort a group more susceptible to allergen-induced asthma.

An elevated serum IgE has been reported to be associated with an increased FEV₁ decline in COPD.^{14,20} In this study, there is evidence to support this, as univariable analysis shows FEV₁ decline to be greater in the group without asthma and an elevated IgE compared to the group with a normal IgE. However, mean FEV₁ percentage of predicted is significantly lower in the group with asthma features and a normal IgE level compared to the group with asthma and an elevated IgE level. Also, the groups are unmatched for age, smoking status, and other variables. Furthermore, the findings do not take into account the interaction of IgE with age, smoking status, bronchodilator response, and asthma on FEV₁ decline.

There is a greater decline in FEV₁ in those with asthma features (≥ 64 mL/yr) than the mean rate of decline previously reported for this cohort (-54 mL/yr),⁵ but less than the mean FEV₁ decline reported for a smaller Danish study.²¹ In a multivariable model (Table 5), age, smoking status, and bronchodilator response are significant determinants of FEV₁ decline but not other features of asthma such as wheezing attacks and an elevated IgE level. Although the observational design of this study creates the possibility of bias, the findings indicate that young individuals with AAT deficiency who smoke and show significant reversibility of airflow obstruction have the highest rate of FEV₁ decline. The most rapid FEV₁ decline occurs at the same age range (30 to 44 years) that subjects report onset of wheezing (mean age, 31 ± 16 years). Therefore, in those who acquire irreversible airflow obstruction, a period of significant bronchial hyperresponsiveness and accelerated loss of lung function may occur early in the natural history. In support of this observation, a report from the Copenhagen Heart Study²² shows that accelerated loss of FEV₁ occurs in subjects with

new-onset asthma. The period of most rapid lung function decline may be missed in those with AAT deficiency newly diagnosed with clinical asthma.

Pretreatment with AAT has been shown to block the development of airway hyperresponsiveness in a model of sheep allergy.²³ Therefore, increasing the local concentration of AAT by augmentation therapy might ameliorate inflammation, reduce bronchial hyperresponsiveness, and prevent the development of chronic airway changes. Accordingly, the groups were divided according to whether augmentation therapy was ever received or not. Overall, multivariable analysis did not show that augmentation therapy is more effective in reducing FEV₁ decline in the groups with asthma compared to the group without. The apparent lack of effectiveness of augmentation for the groups overall is consistent with the findings of the NHLBI registry.⁸ In the registry, subgroup analysis showed augmentation to be most effective in the FEV₁ 35 to 49% category. The definition of asthma in this study is based on simple clinical criteria and lacked any objective measurement of bronchial hyperresponsiveness or airway inflammation that may be important in determining loss of lung function in both asthma and COPD.^{24,25} Significantly, the more severely affected subjects with a lower FEV₁ were more likely to receive augmentation therapy, leading to selection for treatment of those who may have been more susceptible to loss of lung function. This may have limited the power of the analysis to detect a benefit of augmentation therapy in asthma.

In conclusion, features of asthma are common in those with severe AAT deficiency and symptoms may occur early in the course of the development of airflow obstruction. In a small percentage of this cohort, an elevated IgE is associated with a history of allergy and wheezing and is an indicator of atopy. This analysis also shows that an elevated total IgE level is associated with an increased rate of FEV₁ decline but is not an independent risk factor. However, reversible airflow obstruction is common and is an important factor in the accelerated FEV₁ decline seen in young current smokers with AAT deficiency. Asthma as defined in this study is not an independent risk factor for loss of lung function once bronchodilator response, age, and smoking status are considered. In this analysis, augmentation therapy is not more effective in preventing the loss of lung function in those with asthma compared to those without.

ACKNOWLEDGMENT: The authors wish to thank the institutions and investigators that participated in the AAT deficiency registry.⁸

REFERENCES

- 1 Makino S, Chosy L, Valdivia E, et al. Emphysema with hereditary α_1 antitrypsin deficiency masquerading as asthma. *J Allergy* 1970; 46:40–48
- 2 Niggemann B, Albani M. Bronchial asthma and homozygous α_1 antitrypsin deficiency (PI*ZZ) in three members of a family [in German]. *Klin Padiatr* 1989; 201:412–415
- 3 Eden E, Mitchell D, Mehlman B, et al. Atopy, asthma, and emphysema in patients with severe α_1 -antitrypsin deficiency. *Am J Respir Crit Care Med* 1997; 156:68–74
- 4 Tobin MJ, Cook PJJ, Hutchison DCS. α_1 -Antitrypsin deficiency: the clinical, physiological features of pulmonary emphysema in subjects homozygous for PiZ; a survey by the British Thoracic Association. *Br J Dis Chest* 1983; 77:14–27
- 5 Anthonisen NR, Wright EC. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133:814–819
- 6 Berger R, Smith D. Acute bronchodilator changes in pulmonary function parameters in patients with chronic airways obstruction. *Chest* 1988; 93:541–546
- 7 Wiggs BR, Bosken C, Pare PD, et al. A model of airway narrowing in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 145:1251–1258
- 8 The α_1 -Antitrypsin Deficiency Registry Study Group. Survival and FEV₁ decline in individuals with severe deficiency of α_1 -antitrypsin. *Am J Respir Crit Care Med* 1998; 158:49–59
- 9 A registry of patients with severe deficiency of α_1 -antitrypsin: design and methods; The α_1 -Antitrypsin Deficiency Registry Study Group. *Chest* 1994; 106:1223–1232
- 10 Stoller JK, Buist AS, Burrows B, et al. Quality control of spirometry: testing in the registry for patients with severe α_1 -antitrypsin deficiency. *Chest* 1997; 111:899–909
- 11 Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin test reactivity to allergens. *N Engl J Med* 1989; 320:271–277
- 12 Laird NM, Ware JH. Random effects models for longitudinal data. *Biometrics* 1982; 38:963–974
- 13 Tashkin DP, Altose MD, Bleecker ER, et al. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation; The Lung Health Study Research Group. *Am Rev Respir Dis* 1992; 145:301–310
- 14 Sherrill DL, Lebowitz MD, Halonen M, et al. Longitudinal evaluation of the association between pulmonary function and total serum IgE. *Am Rev Respir Dis* 1995; 152:98–102
- 15 Dales RE, Spitzer WO, Tousignant P, et al. Clinical interpretation of airway response to a bronchodilator. *Am Rev Respir Dis* 1988; 138:317–320
- 16 Lorber DB, Kaltenborn W, Burrows B. Responses to isoproterenol in a general population sample. *Am Rev Respir Dis* 1978; 118:855–861
- 17 Piitulainen E, Tornling G, Eriksson S. Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with α_1 -antitrypsin deficiency (PiZZ). *Thorax* 1997; 52:244–248
- 18 Silverman EK, Pierce JA, Province MA, et al. Variability of pulmonary function in α_1 -antitrypsin deficiency: clinical correlates. *Ann Intern Med* 1989; 111:982–991
- 19 Postma DS, Bleecker ER, Amelung PJ, et al. Genetic susceptibility to asthma-bronchial hyperresponsiveness coinherit with a major gene for atopy. *N Engl J Med* 1995; 333:894–900
- 20 Villar MTA, Dow L, Coggon D, et al. The influence of increased bronchial responsiveness, atopy and serum IgE on decline in FEV₁. *Am J Respir Crit Care Med* 1995; 151:656–662
- 21 Seersholm N, Kok-Jensen A, Dirksen A. Decline in FEV₁ among patients with severe α_1 -antitrypsin deficiency type PiZ. *Am J Respir Crit Care Med* 1995; 152:1922–1925
- 22 Ulrik CS, Lange P. Decline of lung function in adults with bronchial asthma. *Am J Respir Crit Care Med* 1994; 150:629–634
- 23 Forteza R, Botkinnikova A, Ahmed A, et al. The interaction of α_1 -proteinase inhibitor and tissue kallikrein in controlling allergic ovine hyperresponsiveness. *Am J Respir Crit Care Med* 1996; 154:36–42
- 24 Lange P, Parner J, Vestbo J, et al. A 15 year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339:1194–2000
- 25 Tashkin DP, Altose MD, Connett JE, et al. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153:1802–1811

Asthma Features in Severe α_1 -Antitrypsin Deficiency*

Edward Eden, Jeffrey Hammel, Farshid N. Rouhani, Mark L. Brantly, Alan F. Barker, A. Sonia Buist, Robert J. Fallat, James K. Stoller, Ronald G. Crystal and Gerard M. Turino

Chest 2003;123; 765-771
DOI 10.1378/chest.123.3.765

This information is current as of July 15, 2009

Updated Information & Services	Updated Information and services, including high-resolution figures, can be found at: http://www.chestjournal.org/content/123/3/765.full.html
References	This article cites 24 articles, 14 of which can be accessed free at: http://www.chestjournal.org/content/123/3/765.full.html#ref-list-1
Citations	This article has been cited by 7 HighWire-hosted articles: http://www.chestjournal.org/content/123/3/765.full.html#related-urls
Open Access	Freely available online through CHEST open access option
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.chestjournal.org/site/misc/reprints.xhtml
Reprints	Information about ordering reprints can be found online: http://www.chestjournal.org/site/misc/reprints.xhtml
Email alerting service	Receive free email alerts when new articles cite this article. sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]