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Asthma and allergy in alpha-1 antitrypsin deficiency

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Summary This study was designed to determine the prevalence of asthma and atopy, in a large group of subjects with alpha-1 antitrypsin deficiency (AATD) participating in the Alpha-1 Foundation Research Registry. A survey was mailed to all Registry participants ($N = 2418$) and results were collated by AATD phenotype. Participants with PiZZ deficiency were compared to PiMZ and other phenotypes by nonparametric statistics. Responses were collected from 757 participants (31%). Overall 44.6% ($N = 338$) reported MD diagnosed asthma. Wheezing was reported in 76% with respiratory infections, activity and exposure to dusts, fumes, and allergens as common triggers. Across the three groups reported asthma with a history of allergies was reported from 20% to 25%. Wheezing symptoms were significantly less common in the PiMZ group compared with other groups. Of those reporting asthma, 83% of the PiZZ group ($n = 192$) also reported another chronic obstructive pulmonary disease (COPD) diagnosis compared to 48% of the PiMZ group ($n = 24$). Asthma as the only reported diagnosis was three times more prevalent in the PiMZ group compared with the PiZZ group. Although asthma diagnosis is imprecise in the presence of COPD, the high prevalence of wheezing to allergen and irritant exposures with symptoms of atopy suggests that asthma is common in AATD but usually associated with COPD. Those with AATD who are susceptible to asthma require allergy evaluation and aggressive anti-inflammatory strategies as part of their management.

Abbreviations: AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease

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Introduction

Alpha-1 antitrypsin deficiency (AATD) is a heterogeneous disorder with a broad spectrum of AAT phenotypes which impart a varying susceptibility to obstructive lung disease and emphysema. Protease inhibitor (Pi) Z is the commonest allele for the homozygous (PiZZ) severe deficiency that significantly increases the susceptibility to lung function loss and emphysema in smokers and nonsmokers.[1] PiMZ, the heterozygous condition, carries only a slightly higher independent risk of obstructive lung disease.[1] The inheritance of an intermediate deficiency state such as PiSZ leads to intermediate susceptibility. Along with the enhanced susceptibility to the development of chronic obstructive pulmonary disease (COPD) may also be an enhanced susceptibility to asthma.

Asthma is the most common respiratory diagnosis in patients with AATD prior to the diagnosis of AATD.[2] In COPD bronchial hyperresponsiveness is associated with a more rapid lung function decline[3] and worse than expected survival.[4,5] This also appears to be true in AATD.[6,7] Furthermore, the presence of asthma increases FEV_1 decline,[8,9] and is a likely independent risk factor for the development of COPD.[10,11] Atopy which predisposes to asthma has also been reported to be more prevalent in those with AATD.[12,13]

Given the potential adverse effects of asthma and atopy in AATD, this study was undertaken to establish the prevalence of these in AATD and to determine the relationship between asthma and COPD in groups with varying severity of AATD.

Methods

The Alpha-1 Foundation Research Registry is a confidential research database established in 1997 by the Alpha-1 Foundation to enroll individuals with AATD and carriers. The Registry is located at the University of South Carolina in Charleston. The Registry is open to those with diagnosed AATD who are invited by mail to join the Registry by submitting an enrollment questionnaire. Enrollment occurs from screening and education programs or through referral from physicians or family members. All Registry participants sign a consent form that was returned to the Registry Center. Over 94% of participants reside in the United States.

The current study consisted of a questionnaire piloted by a small number of AATD patients then mailed to every member of the Registry ($N = 2431$) on 1/15/2004. The questionnaire was based on the ATS DLD 78 used in the NHLBI Registry.[14] Additional questions requested a physician diagnosis, medication history and effectiveness, and a prior history of asthma and allergy. The questions were constructed as commonly asked in clinical practice. Self-reported asthma diagnosis was based on the question "Have you ever been diagnosed by a doctor with asthma?" Self-reported diagnoses of COPD, Emphysema, Chronic bronchitis and Bronchiectasis were made with positive responses to similarly phrased questions. In addition, the diagnosis of chronic bronchitis was made in response to "Do you bring up phlegm on most days for 3 consecutive months or more during the year?" and "How many years have you had trouble with cough and phlegm?" Questions on wheezing were phrased for example as "Do you get attacks of wheezing and whistling in the chest?" Further questions explored precipitating factors and responses to bronchodilators. For questions on allergy participants were asked to enter what they thought they were allergic to and what allergies had been diagnosed by a physician. Questionnaire return was accepted until 3/31/04 when data analysis began. Up to three follow-up telephone calls were made to individuals who reported not knowing their phenotype.

The denominator in percentage calculations was adjusted based on the number of responses to a particular question. Reported percentages were rounded to the nearest whole number. Statistics were performed in SAS (Cary, NC). Different permutations of a clinical definition of asthma were used for intermittently wheezing individuals. These were physician diagnosed asthma with or without concurrent pulmonary diagnoses of COPD, emphysema, chronic bronchitis, and bronchiectasis. The cohort was grouped into severe PiZZ AATD, PiMZ carriers with a mildly reduced AAT and a third "others" group combining PiMS, PiSS, PiSZ and other rare AAT phenotypes with those who did not know their phenotype. The normal approximation to the binomial test and Pearson's χ^2-test was used for the comparison of categorical variables in the current cohort with historical data in the Alpha-1 Registry population. For comparisons within the current cohort, a χ^2-test was applied to categorical variables and ANOVA for continuous variables. P values <0.05 were accepted as significant. For small sample sizes the Wilcoxon Rank Sum test was applied for testing mean differences in continuous variables and the Fisher's Exact test for testing the association between phenotype and each categorical variable.

Results

The questionnaire was returned by 757 individuals (31%). Differences between the cohort returning and not returning the questionnaire are shown in Table 1. The proportions of different phenotypes are significantly different in the current cohort compared with the Registry with significantly less unknown phenotypes. Mean ages for the three groups were 55 ± 13 years, 48 ± 17 years and 52 ± 17 years, respectively. There were 265 nonsmokers (35%), 459 ex-smokers (61%) and 30 current smokers (4%). The frequency distribution of smoking status in the survey cohort was not significantly different from the Registry cohort.

A diagnosis of COPD was reported in 42% ($N = 319$), emphysema in 57%, chronic bronchitis in 28%, and bronchiectasis in 10%. In PiZZ participants COPD was diagnosed in 51% and emphysema in 71%, in PiMZ 20% and 21%, respectively, and in 39% and 54%, respectively, in ''others'' group.

Prevalence of self-reported asthma

A physician diagnosis of asthma was reported in 45% ($N = 338$) of the cohort. An asthma diagnosis occurred in 50% of PiZZ individuals, 31% of PiMZ individuals and 42% of others. The mean age for asthma diagnosis was 38 ± 18 years in PiZZ, 30 ± 18 years in PiMZ and 35 ± 19 years in ''others'' group.

''Ever wheezing or whistling in the last 12 months'' was reported in 76%. Ever wheezing was reported in 81% of PiZZ, 61% of PiMZ and 79% of other phenotypes ($P < 0.0001$).

Except for allergy contact the prevalence of wheezing symptoms are significantly different between phenotypes (Table 2). Self-reported factors associated with asthma attacks were reported

Table 1 Characteristics of study participants compared to registry participants.

	Registry total ($N = 2431$)	Study cohort ($N = 757$)	P-value
Phenotype			<0.0001*
PiZZ	1337 (55%)	458 (61%)	
PiMZ	459 (19%)	164 (22%)	
PiSZ†	84 (4%)	32 (4%)	
Other phenotypes†	74 (3%)	11 (1%)	
Not known†	477 (20%)	92 (12%)	
% Reporting asthma	842 (35%)	338 (44%)	<0.0001‡
Nonsmokers	867 (36%)	265 (35%)	NS§

*The normal approximation to the binomial test was applied.
†Categories combined into a single ''other'' group.
‡Pearson's χ^2-test was used.
§NS = Not significant at a level of 0.05.

Table 2 Affirmative responses to questions on wheezing symptoms by AATD phenotype.

Characteristics of wheezing	PiZZ	PiMZ	Other phenotypes	P-value*
Wheezing in past 12 months?	67%	41%	62%	<0.0001
Wheezing days in the last 12 months? (mean $\pm$ SD)	71 ± 110	56 ± 95	62 ± 100	NS
Wheezing with a cold?	66%	46%	70%	<0.0001
Wheezing apart from a cold?	56%	39%	57%	0.0004
Wheeze most days?	16%	9%	19%	0.035
Wheezing attacks disturb sleep?	18%	15%	24%	NS
Wheezing during or after activity that causes shortness of breath?	56%	40%	58%	0.0015
Wheezing after dusts, fumes, strong smells?	52%	33%	53%	<0.0001
Wheezing after contact with allergy?	33%	31%	33%	NS

*χ^2-tests were applied for categorical variables and ANOVA for the continuous variable.

as fumes and strong odors, cold air, exercise, emotions and allergies.

Asthma symptoms and diagnosis as related to smoking status

In 265 nonsmokers 62% reported ever-wheezing whereas in 489 either ex-smokers or current smokers, 84% reported ever-wheezing ($P<0.001$ by χ^2). Of nonsmokers, 37% reported asthma compared with 49% in current smokers or ex-smokers. For reported asthma in the PiZZ group 46% were nonsmokers vs. 52% were ex- and current smokers, in the PiMZ group 26% nonsmokers vs. 36% ex- and current smokers reported asthma and in the ''others'' group 33% vs. 46%, respectively. The percent of nonsmokers was significantly greater in the PiMZ group than in the other groups (Table 3).

Current smokers or ex-smokers with a physician diagnosis of asthma were more likely to report both emphysema and chronic bronchitis than in nonsmokers (41% vs.18%, respectively). Isolated self-reported asthma was more common in non-smokers, 48%, than in current smokers or ex-smokers, 14%. The frequency distribution among different asthma conditions (never wheezing with isolated asthma, wheezing with isolated asthma, wheezing with asthma and other diseases) is significantly different between nonsmokers and smokers (χ^2 P-value <0.0001).

Past history of asthma

For asthma attacks that had occurred greater than 1 year prior to completion of the questionnaire, in response to the question ''In the past, have you ever had an attack of wheezing that has made you feel short of breath'', 45% of PiZZ, 38% of PiMZ and 41% of other phenotypes answered affirmatively. Table 3 shows details of symptoms and family history in the 323 participants answering affirmatively according to phenotype. It is notable that the time from the first wheezing attack to diagnosis is reported as 7 years in the PiZZ group.

History of atopy

As atopy is a risk factor for asthma, respondents were asked a series of questions on the presence, type and treatment of allergies (Table 4).

In order of frequency, dust and dust mites, pollen, animals and molds were mentioned as allergens. In general, specific allergens causing respiratory symptoms were reported more frequently by patients than were diagnosed by physicians.

Table 3 Past medical history of wheezing attacks, asthma and smoking by AATD phenotype.

Past history	PiZZ	PiMZ	Other phenotypes	P-value*
Age asthma diagnosed, years (Mean ± SD)	39 ± 16	28 ± 18	33 ± 19	0.0017
Age at 1st attack, years (Mean ± SD)	32 ± 15	26 ± 16	31 ± 18	NS
2 or more attacks?	92%	92%	93%	NS
Inhaler use to treat attacks?	87%	82%	84%	NS
Relief of attack within 30 min?	80%	73%	82%	NS
Are wheezing attacks still present?	69%	60%	84%	0.018
Age if stopped, years (Mean ± SD)	46 ± 14	35 ± 16	51 ± 12	NS†
Family with asthma?	56%	76%	67%	0.014
Nonsmokers	26%	50%	20%	0.0003

*χ^2-tests or Fisher Exact tests were applied for categorical variables and ANOVA for continuous variables.
†Wilcoxon Rank Sums test.

Table 4 Affirmative responses to questions related to allergy by AATD phenotype.

Variable	PiZZ (%)	PiMZ (%)	Other phenotypes (%)	P-value[a]
Do you have allergies?	58	63	53	NS
Did an MD tell you?	35	45	34	NS
Do you take meds for allergies?	27	33	30	NS
Have you received allergy shots?	14	18	14	NS

[a]Chi-square tests were applied for categorical variables and ANOVA for continuous variables.

Table 5 Univariate comparisons of affirmative responses to questions about asthma and wheezing attacks by augmentation usage in subjects with the PiZZ phenotype (Total 443 subjects).

Variable	No augmentation ($N = 136$)		Augmentation ($N = 307$)		P-value[‡]
	Cases*	%[†]	Cases	%	
Diagnosed asthma by MD	60	44	166	54	0.05
Ever wheeze	94	69	268	87	<0.0001
Wheezing in past 12 months	73	54	228	74	<0.0001
Wheezing with cold	73	54	223	73	<0.0001
Wheezing after allergy contact	38	28	106	34	NS
Attacks immediately after activity	63	46	186	61	0.005
Attacks from dust/fumes/strong smells	59	43	173	56	0.01

*Number of respondents with affirmative responses to the variable.
[†]Percentage of cases over nonmissing responses.
[‡]χ^2-tests were applied.

The percentage of participants with physician diagnosed asthma self-reporting allergies was 92% for PiZZ, 94% for PiMZ and 96% for ''others''. In contrast, within each group, the percentage reporting physician diagnosed allergy and asthma was less: 49% of PiZZ, 64% of PiMZ and 58% of ''others''.

Medication therapy for asthma

The time to effective relief of bronchospasm by bronchodilator therapy was not significantly different between those reporting asthma compared with those reporting COPD. In the PiZZ group, for those reporting emphysema the mean time for bronchodilator response was 8.0 ± 8 min compared to 7.6 ± 6 min for those reporting asthma and 14.7 ± 57 min for those reporting both asthma and emphysema.

In participants with physician diagnosed asthma, 34% of PiZZ, 10% of PiMZ and 25% of ''others'' reported that augmentation therapy for AATD helped their asthma symptoms. Table 5 compares augmentation use in PiZZ and PiMZ groups as related to asthma diagnosis and wheezing symptoms. The percentage of current and ex-smokers was significantly greater in the augmentation group compared to the group without augmentation use ($P < 0.001$) (data not shown).

Overlap of reported asthma and COPD

A nonproportional Venn diagram Fig. 1A illustrates the diagnostic overlap in the cohort. Forty-six percent of respondents reporting ever wheezing did not report a physician diagnosis of asthma. In participants reporting asthma, 27% did not report an additional diagnosis of emphysema and or chronic bronchitis, 34% reported all three conditions. Of interest 7% reporting asthma did not report wheezing whereas 19% reporting wheezing did not report asthma, chronic bronchitis or emphysema.

Figure 1B indicates that in the PiZZ group 83% of those reporting asthma also reported another COPD diagnosis. In contrast, of the PiMZ group 48% of those reporting asthma reported another COPD diagnosis (Fig. 1C). In this group, 23% indicated that they had ever wheezed but did not report any COPD diagnosis compared to 12% in the PiZZ group. Comparison of asthma only and ever wheezing indicates a significantly greater prevalence in the PiMZ compared to the PiZZ group (Pearson χ^2-test $P < 0.001$). The estimated ratio of prevalence was 3.2 (95% confidence limit 1.8–5.7).

In asthma diagnosed by a physician and self-reported but without COPD, the mean age of asthma diagnosis was significantly less in the PiMZ group (26 ± 15, $N = 20$) compared to the PiZZ group (47 ± 16, $N = 23$) ($P = 0.003$) but other self-reported variables were not significantly different.

Discussion

This study was designed to estimate the prevalence of asthma and allergy in a large cohort with AATD participating in the Alpha-1 Foundation Research Registry. Asthma is a risk factor for an accelerated decline in FEV_1.[3,6,7] In a 20-year follow-up study from Tucson,[10] physician diagnosed asthma is a risk factor for COPD with the length of time to asthma diagnosis an additional independent risk factor. To prevent this increased susceptibility to the loss of lung function over and above that induced by AATD

itself, the recognition and treatment of asthma in AATD is paramount. Unfortunately, results from this study suggest that the time from symptom development to the diagnosis of asthma may be delayed in severe AATD (Table 3).

The results indicate that 44% of participants report a physician diagnosis of asthma. The current estimate is higher than the previously reported 21%[6] because of the likely higher questionnaire return rates from individuals with asthma interested in answering questions about asthma. Also ATS/ERS guidelines[1] recommend AATD testing on those with asthma that is not completely reversible increasing the potential for recruitment bias in asthmatics. The findings are however supported by prior observations[12,13] which suggest an association between asthma in severe AATD. In this study, approximately one-third of PiMZ subjects report a physician diagnosis of asthma and over 44% with physician diagnosed allergies. These findings add support to the controversial association between the PiMZ phenotype asthma and atopy.[1]

In COPD, wheezing is common and spirometric bronchodilator responsiveness, a characteristic of asthma, is more prevalent as % FEV_1 declines.[9,15] In this cohort, current smokers or ex-smokers with a physician diagnosis of asthma are more likely to be also diagnosed with emphysema and/or chronic bronchitis than nonsmokers (41% vs.18%, respectively). Asthma diagnosis and asthma symptoms are reported significantly more often in PiZZ participants receiving augmentation therapy in whom COPD tends to be more severe.[14] Therefore, the spectrum of airflow obstruction in AATD includes asthma symptoms but the diagnosis as the cause of symptoms is likely to be imprecise because of overlapping features of asthma and COPD.

Certain aspects of the medical history may support a diagnosis of asthma in the presence of COPD. Asthma is associated with defined triggers of attacks such as viral infections, dusts, fumes and allergens and a positive family history. In this cohort, wheezing attacks appear to be associated with a COPD diagnosis especially in the PiZZ group. Triggered wheezing attacks are generally less frequent in PiMZ individuals, a group with less COPD and emphysema, but still occur in up to 46% (Table 2). It is also notable that a family history of asthma was reported commonly in the three groups

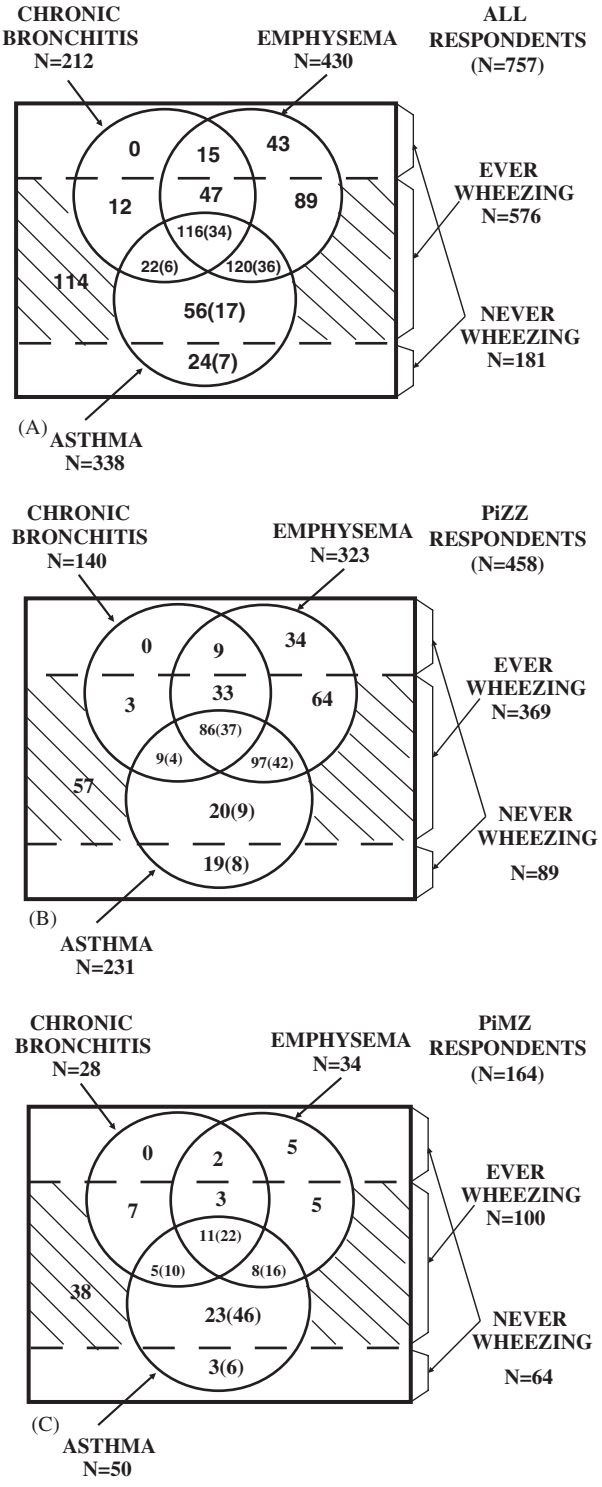

Figure 1 (A) shows a nonproportional Venn diagram for the Registry participants to indicate the proportion of subjects reporting one or more COPD conditions. The box represents the total cases. The diagrams are further subdivided according to whether or not ever wheezing was reported in the questionnaire. The three circles within represent chronic bronchitis, emphysema and asthma. The numbers in each area indicate the number of participants in each category. Numbers in parentheses show the percentage of participants reporting asthma in each category. (B) As above but for participants with the PiZZ phenotype. (C) As above but for participants with the PiMZ phenotype.

but to some extent is likely to be an overestimate due to the overlap of COPD with asthma in families with AATD.

Atopy confers a genetic predisposition to asthma[16] and this study supports a previous study,[13] where positive skin reactions to common aeroallergens occurred in 48% in a group with severe AATD and COPD compared with 28% in COPD controls. In atopy, a reduced level of AAT may also enhance the severity of airway hyperresponsiveness.[17] The diagnosis of allergy is often made by patients and physicians without confirmatory testing and may not be accurate. For example in participants with a physician diagnosis of asthma, self-reported allergies were almost universally present in the three groups whereas physician diagnosed allergy and asthma was less (49–64%) but still occurred commonly. Allergen-induced wheezing was reported in about a third and appeared independent of AATD severity (Table 2). Immunotherapy may be offered as a treatment option but only a small percent reporting allergen sensitivity received immunotherapy. Therefore, an allergy evaluation, with avoidance of triggers, should be an important part of the management of those with AATD who describe wheezing attacks triggered by allergen exposure.

A comparison of reported asthma was made between PiMZ and PiZZ groups who did not report an additional diagnosis of COPD. First, the prevalence of reported asthma in the absence of COPD was 3 times greater in the PiMZ group than in the severe AATD group. This finding is not unexpected as COPD is much less common in the heterozygous group. Second, the age of reported asthma diagnosis in the PiMZ group is similar to previously reported large studies[18] and significantly less than in this PiZZ subset. The younger age in the PiMZ group suggests the presence of asthma without COPD. Asthma alone also occurs in those with the severe deficiency before the development of COPD. In a prospective cohort study,[19] an asthma prevalence of 15% was reported in 129 PiZZ subjects with normal lung function followed for the first 22 years. In most with severe AATD, however, asthma is diagnosed at a later age when COPD has already developed.

The reported data are subject to physician and participant bias. For example 13% of those never reporting a wheezing attack report a physician diagnosis of asthma and 6–8% of participants are diagnosed with asthma but never wheeze. Also 15–23% report ever wheezing without reporting any physician diagnosis. Lack of an objective measurement for asthma leads to bias in diagnosis[20] and lack of patient reporting may hamper efforts to identify those with AATD early in their disease. Asthma is the most common respiratory diagnosis in patients with AATD prior to the diagnosis of AATD.[2]

A major finding in this study is the high prevalence of self-reported wheezing with allergen and irritant exposures. Physician diagnosed asthma and allergies are also reported commonly in AATD. Asthma is difficult if not impossible to distinguish clinically from COPD in those with established airflow obstruction. Given the overlap between asthma and COPD in this population and the potential impact of asthma on FEV_1 loss, evaluation of the wheezy patient with AATD should include allergy testing and aggressive treatment to reduce bronchial hyperresponsiveness.

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