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ORIGINAL RESEARCH

The Prevalence of Alpha-1 Antitrypsin Deficiency Among Patients Found to Have Airflow Obstruction

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Abstract

Introduction: **Alpha-1 antitrypsin deficiency (AATD) is a genetic disease that may be manifested by chronic obstructive pulmonary disease. Despite professional society guidelines that recommend broad testing of at-risk individuals, fewer than 10% of affected individuals have been identified. The goals of this study were to estimate the frequency of abnormal AAT genotypes among patients found to have fixed airflow obstruction and to assess the feasibility of having Pulmonary Function Laboratory personnel administer the study.** ***Methods:*** **Nineteen medical centers in the United States participated in the study. Eligible patients (> GOLD II, FEV_1/FVC ratio < 0.7, with post-bronchodilator FEV_1<80% predicted) were offered testing for AATD by the Pulmonary Function Laboratory personnel at the time of pulmonary function testing.** ***Results:*** **A total of 3,457 patients were tested, of whom 3152 were eligible. Deficient patients (ZZ, SZ) constituted 0.63% of subjects, while 10.88% were carriers (MS, MZ). Neither demographic (except African-American race) nor post-bronchodilator pulmonary function variables (FEV_1, FVC, FEV_1/FVC ratio, TLC, and FEV_1/FVC) allowed us to predict AAT heterozygote or deficiency status.** ***Conclusions:*** **The prevalence of AATD among patients undergoing pulmonary function tests with fixed airflow obstruction was 0.63%. Pulmonary Function Laboratory personnel effectively conducted the study.**

Abbreviations

AAT	Alpha-1 Antitrypsin
AATD	Alpha-1 Antitrypsin Deficiency
ATS	American Thoracic Society
DLCO	Carbon Monoxide Diffusing Capacity
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
PFT	Pulmonary Function Test
RT	Respiratory Therapist
RV	Residual Volume
TLC	Total Lung Capacity

Keywords: Alpha 1-Antitrypsin Deficiency, Spirometry, Respiratory Care, Chronic Obstructive Pulmonary Disease, Pulmonary Function Test.

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Introduction

Alpha-1 antitrypsin (AAT) deficiency is a common genetic disorder in the United States, with an estimated prevalence of 60,000–100,000 individuals with severe AAT deficiency (AATD) (1). However, fewer than 10% of these individuals have been diagnosed (2,3). In this context and driven by the

observation that 2–3% of all patients with COPD have been found to have severe AATD in early series (4,5), official professional society recommendations (from the American Thoracic Society, American College of Chest Physicians, European Respiratory Society, and American Association for Respiratory Therapists) have endorsed AAT testing for all symptomatic adults with fixed airflow obstruction on pulmonary function tests (6).

Despite these recommendations, AATD remains under-recognized. For example, studies assessing the diagnostic delay interval between first symptom of AATD and initial diagnosis indicate a lag of 6.3–7.2 years. (7,8) Also, in an early study of detection practices, 44% of AAT deficient respondents reported seeing at least 3 physicians before the initial diagnosis of AATD was made (9) and more recent analyses suggest no shortening of the diagnostic delay for recently diagnosed individuals (7). Although the issue has not been specifically studied in AATD, physicians' general disinclination to adopt guidelines may be at the core of this ongoing challenge in diagnosis (10).

As an alternative strategy to enhance detection of AAT deficiency, we hypothesized that respiratory therapists (RTs) or pulmonary function technicians could enhance the frequency of testing for and recognition of AAT deficient individuals. Specifically, we conducted the current prospective multicenter study to assess the frequency with which eligible individuals (i.e., those without prior known AAT status who were undergoing routinely scheduled pulmonary function testing and found to have fixed airflow obstruction) were both tested for and found to have AATD. Because RTs and pulmonary function technicians conducted the patient recruitment and testing, a secondary goal of the study was to assess RTs' and PFT technicians' effectiveness to administer this study.

Table 1. Recruitment by clinical center

Clinical Center	Enrollment
Atlanta VA Medical Center	64
Cleveland Clinic	128
Cleveland Clinic Florida	178
Emory Crawford Long Hospital	9
Emory University	35
Hospital Municipal de San Juan	80
Mayo Clinic	766
Medical University of South Carolina	365
Miami VA Medical Center	189
National Jewish Medical and Research	463
Oregon Health and Science University	50
St. Luke-Roosevelt Hospital Center	184
University of California Los Angeles	60
University of Chicago	268
University of Florida (Gainesville)	167
University of Florida (Jacksonville)	18
University of Miami	43
University of North Carolina	132
University of Texas	258
Total	3457

Methods

The study was approved by the Institutional Review Boards of the 19 participating academic medical centers (Table 1). Eligible study subjects were adults (age ≥18 years) without prior knowledge of their AAT status who were found to have COPD GOLD Stage II-IV (FEV1 <80 % predicted with FEV1/FVC ratio <0.7) based on post-bronchodilator pulmonary function tests (PFTs) ordered by their managing physicians and conducted in the PFT laboratories of participating institutions. Spirometry testing was required for study participation; some subjects underwent additional PFTs (e.g., lung volumes, diffusing capacity measurements, etc.).

From July 2007 to December 2009, consecutive eligible subjects were invited to participate. Importantly, the study coordinators at each site were RTs or pulmonary function technicians, who conducted the PFTs on potential subjects and approached eligible study candidates, consented interested subjects, and evaluated their study qualification by reviewing inclusion and exclusion criteria. All PFTs were performed in accordance with American Thoracic Society standards (11) and included post-bronchodilator testing. Values from NHANES III (12) were used as the reference standard for enrollment if available at each study site. If this reference standard was not available locally, the site used their local reference standard and all percent predicted values were recalculated centrally at the Data Coordinating Center using NHANES III.

Subjects who consented to participate also underwent genotyping for AATD and were administered a brief survey (to assess demographic features, family history, and baseline smoking history). These assessments were also administered by RTs or pulmonary function technicians. Genotyping was conducted using dried blood spot card test kits (13) in which the eluted blood underwent polymerase chain testing for the S and Z AAT alleles at a central laboratory (Alpha-1 Genetics Laboratory at the University of Florida, Gainesville, FL). Severity of COPD was classified according to GOLD criteria (14). A consort diagram is presented in Figure 1. Sixty-two individuals were misclassified based on the assessment of the sites and were found to have GOLD classes bellow II after central calculation of FEV_1 % predicted according to the NHANES III reference standard. All of these individuals were genotyped and were not found to be deficient.

Sample size calculations were performed based on a one-sided test of proportion using Clopper-Pearson binomial confidence intervals, an assumed population proportion of $p = 0.01$, and a 0.95 confidence level. This yielded a minimum sample size of 2436 (15–17).

Demographic variables were summarized with descriptive statistics and then analyzed using chi-square tests, logistic regression, and Wilcoxon scores analysis of variance. The association of lung function variables with AAT heterozygote and deficiency status was evaluated

using logistic regression. Data were analyzed using SAS version 9.2 (SAS, Cary, NC).

Results

A total of 3,457 subjects were recruited from 19 academic centers (range 9 to 766 subjects/center). Table 2 presents the characteristics of participating subjects. Twenty subjects (0.58% of 3457) were found to have genotypes AAT types ZZ or SZ, and were considered to have severe deficiency of AAT. A total of 343 heterozygotes (9.92 %) characterized as MZ (n = 124) and MS (n = 225) were also detected. Excluding the 62 subjects (all with normal AAT levels) who were tested but later found to have GOLD 1 COPD based on central recalculation of the FEV_1 % predicted, 1 patient missing a genotype, and 242 patients with incomplete data preventing GOLD classification, 3152 eligible subjects remained, of whom 0.63% were found to have severe AATD and 10.88% were MZ or MS heterozygotes.

Univariate analysis of demographic features of AAT deficient (ZZ, SZ) vs. heterozygotes (MZ,MS) and normal (MM) subjects showed no significant differences that would suggest an enriched yield group for testing, other than a previously recognized (1) lower rate of AAT deficiency among African-American subjects.

Table 3 presents the genotype distribution by GOLD stage. Though there were more deficient patients in GOLD stage III than in stages II or IV, this difference did not achieve statistical significance.

No association was found between the post-bronchodilator spirometry variables FEV_1 and FVC and AAT heterozygote or deficiency state. Post-bronchodilator FEV_1/FVC was negatively associated with (p = 0.0313) AAT heterozygote or deficiency state. Total lung capacity and RV and were positively (p = 0.0002 and p = 0.0060, respectively) associated with having a carrier or AAT deficiency state.

Discussion

The main finding of the current study of targeted detection of AATD by respiratory therapists is that 0.63% of 3152 eligible subjects were found to have a severe deficiency genotype. Another 10.88% of subjects were found to be heterozygous for the Z or S allele. Also, this study establishes the feasibility and effectiveness of RTs or PFT technicians as study coordinators capable of

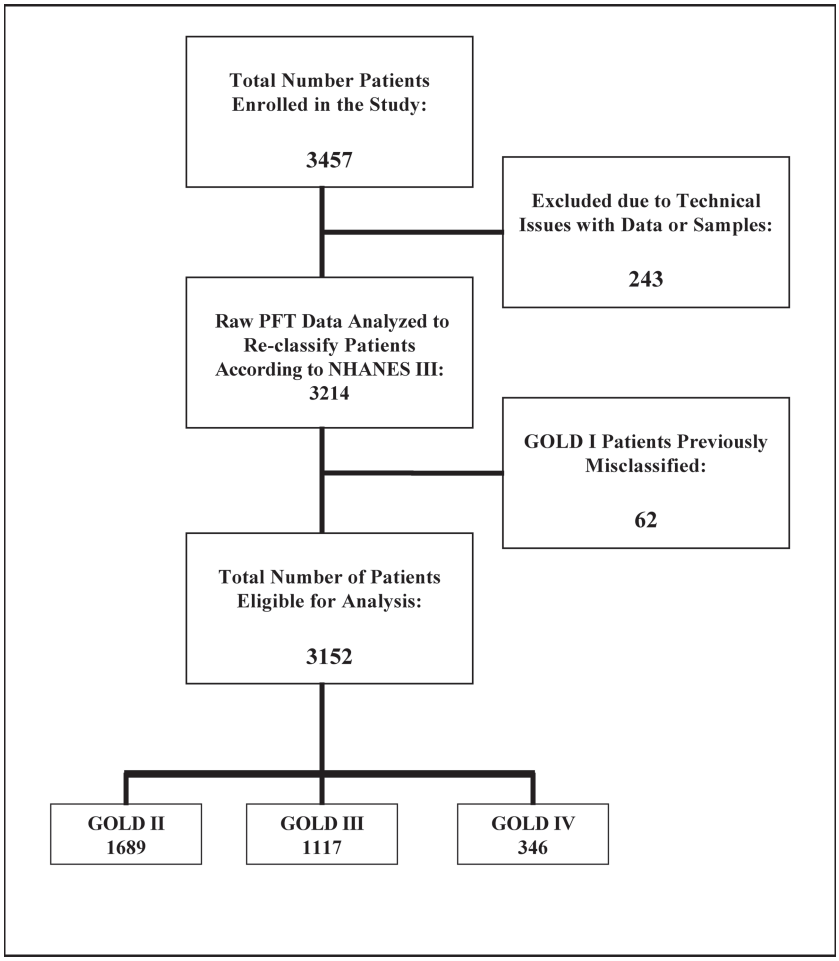

Figure 1. Consort Diagram of the Study

Table 2. Characteristics of participating subjects

	Normal (MM)	Mild (MS,MZ,SS)	Severe (SZ,ZZ)	
	N = 2780	N = 352	N = 20	*p*-Value
Age (Mean (SD))	63.8 (12.3)	64.5 (11.2)	58.0 (10.3)	0.6515
Female (%)	44.2	41.2	20.0	0.1202
Race (%)				**<.0001**
Caucasian	78.4	88.6	95.0	
African American	14.5	4.3	0.0	
Asian	0.5	0.0	0.0	
Other	6.6	7.1	5.0	
Smoke Ever (%) (N = 3141)	81.2	86.3	80.0	**0.0284**
Smoke Now (%) (N = 2606)	26.1	23.5	11.1	0.1955
Avg Cig Packs Per Day * Years Smoked (Median (Q1, Q3)) (N = 2501)	43 (27, 64)	44 (27, 63)	31 (20, 50)	0.7739
PreFEV (Mean (SD))	1.3 (0.6)	1.3 (0.5)	1.4 (.6)	0.6458
Pre FVC	2.6 (0.9)	2.7 (0.9)	3.0 (1.0)	0.3454
Pre FEV_1/FVC	0.50 (0.1)	0.49 (0.1)	0.45 (0.1)	**0.0313**
Pre TLC	6.3 (1.6)	6.7 (1.6)	7.7 (1.9)	**0.0002**
Pre RV	3.5 (1.3)	3.8 (1.4)	3.9 (1.7)	**0.006**
Pre RV/TLC	0.6 (0.1)	0.6 (0.1)	0.5 (0.2)	0.9232
Pre DLCO	56.6 (22.9)	52.9 (22.9)	54.5 (31.1)	0.1046
Post FEV	1.5 (0.6)	1.4 (0.5)	1.5 (0.5)	0.7478
Post FVC	2.8 (0.9)	2.9 (0.9)	3.2 (0.9)	0.1303
Post FEV_1/FVC	0.51(0.1)	0.50 (0.1)	0.46 (0.1)	**0.0187**

Abbreviations: Pre = Pre bronchodilator; Post = Post Bronchodilator; DLCO = Carbon Monoxide Diffusing Capacity; FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; GOLD = The Global Initiative for Chronic Obstructive Lung Disease; PFT = Pulmonary Function Test; RV = Residual Volume; TLC = Total Lung Capacity.

conducting a multicenter PFT Laboratory-based AAT detection effort.

These results extend prior targeted detection efforts and show a generally lower prevalence of severe deficiency and heterozygous genotypes than many earlier studies (4,18,19,19–26) (see Table 4, adapted from Aboussouan and Stoller (27)). Specifically, 4 earlier studies of targeted detection have shown prevalences of ZZ individuals exceeding the rate of 0.63% in the current study (i.e., 1.9%, 3.2%, 7.3%, and 9.9% (4,22–24). Similarly, while several earlier targeted detection studies have reported lower rates of detecting individuals with MZ and MS genotypes (Table 4), others have reported higher rates of detection for MZ (7.7%, 17.9%, and 18.1%, respectively) and MS (6.6%, 7.1%, and 10.1%).

Although the precise reason for the broad range remains unclear, possible reasons include differences in AAT testing methods, differences in how potential subjects were identified, and in the target populations themselves in these various studies. It is noteworthy that, unlike some earlier studies with higher detection rates, the current study did not include an accompanying awareness campaign (19).

To the extent that the detection frequencies in our study generally resemble those by Wencker et al. (18) in a study testing patients with COPD, asthma, and bronchiectasis, it is perhaps not surprising that the specific detection rates are sensitive to the specific criteria used to determine in whom AAT testing should be conducted. This study reports the largest targeted detection study presented to date that implements the testing criteria advocated in the American Thoracic Society/European Respiratory Society guidelines on AATD and does so in a way that simulates clinical practice (i.e., patients undergoing PFTs for symptoms are those that clinicians will see and should be tested).

Because the known AATD patients were excluded we suggest that the rates reported herein may predict the rates of detection in the subgroup of referred COPD patients that would be observed if the practice standards recommended in those guidelines were more widely adopted. At the same time, it is possible that the detection estimates in this study may underestimate those from more general practice because all the centers participating in this study have generally had a long-standing interest and awareness of AATD. As a result, because the eligible patient pool for this study excludes cases of known severe AATD, a number of potentially eligible subjects may have been excluded due to prior AAT testing at the participating center (because of prior AAT awareness).

In this way, the pool of patients likely to be detected in this study would be limited to only "incident" cases of AATD (i.e., those presenting to the center for the first time) and would therefore likely underestimate the combined frequency of "prevalent" and "incident" cases. Other reasons for a lower detection rate may be related to the methodology of this project. The patients eligible for screening were selected among COPD GOLD class II and above, and therefore the estimate of prevalence using this methodology excludes AATD patients with mild COPD. The prevalence of AATD in patients with GOLD I is not known. In addition, the project used a simple definition for obstruction and did not include more elaborate definitions and algorithms that address

Table 3. Alpha-1 Antitrypsin Genotype Distribution by COPD GOLD Stage

GOLD Class	Genotype			
Frequency Percent Row % Col %	1-Normal(MM)	2-Mild (MS,MZ,SS)	3-Severe(SZ,ZZ)	Total %
II	1506 47.78 89.17 54.17	175 5.55 10.36 49.72	8 0.25 0.47 40.00	**1689** 53.59
III	972 30.84 87.02 34.96	136 4.31 12.18 38.64	9 0.29 0.81 45.00	**1117** 35.44
IV	302 9.58 87.28 10.86	41 1.30 11.85 11.65	3 0.10 0.87 15.00	**346** 10.98
Total %	**2780** 88.20	**352** 11.17	**20** 0.63	**3152** 100.00

issues of age and gender in defining true obstruction based on spirometry (28).

Prior studies in COPD have been limited by biases resulting from studying only a population that has been referred for spirometry. The generalizability of conclusions from the current study may be similarly limited by our studying only COPD patients in GOLD Stages II–IV who were referred for spirometry. Also, participating centers were geographically clustered, potentially limiting the generalizability of the study results to the entire United States (29–31). Also with great variation in numbers of patients recruited by participating centers, the possibility of a center effect cannot be excluded.

Table 4. Summary of previous AATD detection efforts

First Author	Detection Strategy	Number of Patients	Prevalence of Specific AAT Phenotype (%)					
			PI*ZZ	PI*SZ	PI*MZ	PI*SS	PI*MS	Other
Targeted detection (other than by Spirometric Criteria)								
Bals (19)	Case-finding linked to an AATD awareness program	2696 (Germany)	9.9	2.0	18.1		3.6	Rare phenotype 0.5
Luisetti (23) Ferrarotti (33)	Case-finding (missing or reduced α1 globulin band, early onset emphysema, familial cluster, first degree relative of subjects with ascertained AATD or MZ heterozygosity)	2127 (Italy)	7.3	1.9	17.9	0.05	6.6	Null Null 0.4 Z null 0.2 Rare variants 0.2
Lieberman (4)	Case-finding (Patients with advanced COPD admitted for carotid body surgery)	965 (US)	1.9	0.3	7.7	0.3	10.1	
Corda (21)	Case-finding (Emphysema without risk factors or of early-onset, spontaneous pneumothorax, cervical artery dissection, PAS positive bodies in liver, isolated transaminase elevation, ANCA positive, or low alpha-1 proteins on protein electrophoresis)	285 (Italy)	12	8	62		14	PI*ZI 0.35, PI*ZM malton 0.35 PI*MM malton 2.1
Detection in Patients with Obstructive Diseases								
Brantly (22)	Case-finding (Targeted detection in COPD with education program and free testing)	969 (Florida)	3.2	0.4	11			
de la Roza (20)	Case-finding (Patients with COPD)	2137 (Spain)	0.37	0.14		0.14		
Wencker (18)	Targeted detection (Patients with COPD, emphysema, asthma, or bronchiectasis)	1060 (Germany)	0	0.2	3.7	0.09	3.4	PI*M Null 0.09
Matzen (25)	Case-finding (Individuals with abnormal PFTs)	225 (US)	0		2.7		7.1	PI*FF 0.4
Rahaghi (26)	Case-finding in GOLD II-IV sent for Spirometry tested after alert addended to reports	29 (US)	0		1			
Rahaghi (current study)	Case-finding in GOLD II-IV sent for Spirometry-excluded previously tested patients	3152 (US)	0.32	0.32	3.87	0.25	7.01	

Other than finding an expectedly lower rate of severe AATD among African-Americans, the study's inability to identify an "enriched" subset of patients in whom the frequency of AATD is higher than others with fixed airflow obstruction warrants comment. For example, although the failure of subset analyses to identify an enriched population could reflect the low rate of detecting AAT deficient individuals in this population overall (0.63%) and the resultant low power of the study to discriminate between subsets, an alternative possibility is that no such enriched subsets exist.

To the extent that the latter explanation pertains, our findings can be interpreted to validate the broad recommendations in available AATD guidelines that all symptomatic adults with fixed airflow obstruction on pulmonary function tests should undergo AAT testing once. The yield of this routine screening of COPD patients is relatively high compared with other routinely performed laboratory tests conducted in targeted detection efforts (32).

In establishing the feasibility of employing RTs and pulmonary function technicians as study coordinators for a large, multicenter trial, several study findings are also noteworthy. For example, only 2% of recruited subjects were misclassified for study inclusion, some of whom were ultimately deemed ineligible because they were found to have GOLD 1 COPD by central calculation of FEV_1 % predicted according to the NHANES III reference standard. This low rate of misclassification by RTs and PFT technicians as study coordinators extends the results of an earlier, single center study in which RTs were reported to misclassify 3.3% of subjects for study participation.(26) In addition to correctly identifying eligible subjects, RTs effectively explained the study protocol and basics of AATD to eligible subjects and conducted AAT testing using the finger stick test kits.

Conclusions

In summary, in the context that AATD remains underrecognized, the results of this targeted detection study reinforce the value of complying with American Thoracic Society/European Respiratory Society guidelines by testing broadly among adults with fixed airflow obstruction and suggest that RTs and pulmonary function technicians can effectively conduct such research and testing.

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Declaration of Interest

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Institutions where the study was undertaken:
The Atlanta VA Medical Center, GA
Cleveland Clinic
Cleveland Clinic Florida
Emory Crawford Long Hospital
Emory University
Hospital Municipal de San Juan
Mayo Clinic
Medical University of South Carolina
Miami VA Medical Center
National Jewish Medical and Research
Oregon Health and Science University
St. Luke-Roosevelt Hospital Center
University of California Los Angeles
University of Chicago
University of Florida (Gainesville)
University of Florida (Jacksonville)
University of Miami
University of North Carolina
University of Texas

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