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Short Communication

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Alpha-1 Antitrypsin Phenotyping: An Unmet Educational Need of Healthcare Providers

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Abstract

Background: Diagnosing alpha-1 antitrypsin deficiency (A1ATD) involves two-step laboratory testing, determination of serum alpha-1 antitrypsin (A1AT) level and phenotyping if A1AT < 100 mg/dL. Whether these guidelines are effectuated in clinical practice is uncertain. To begin to address this issue, we determined whether A1AT phenotyping is performed in patients with serum A1AT 57 - 99 mg/dL at our institution.

Methods: We reviewed the medical records of patients seen at Jesse Brown Veterans Affairs Medical Center from January 2019 to October 2022 with serum A1AT between 57 and 99 mg/dL. In each case, pertinent demographic, clinical, and pulmonary function tests data were extracted. Data were presented as means and standard deviation (SD) where appropriate. The Student's *t*-test was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results: Thirty patients (90% males; 60 ± 18 years) with serum A1ATD < 100 mg/mL were identified. Fourteen were African Americans, four Hispanics, and 12 non-Hispanic Whites. The majority were current or ex-smokers. Fourteen (47%) patients had lung disease, 14 (47%) liver disease and one had concomitant lung and liver diseases. Mean ± SD forced expiratory volume in 1 s (FEV_1) and lung diffusing capacity were 2.57 ± 1.41 L (67±19% predicated) and 18.7 ± 10 mL/min/mm Hg (64±28% predicted), respectively. Only 13 patients (43%) underwent phenotype testing (seven African Americans, five Whites, and one Hispanic). Six patients had MZ phenotype, four MS, and three SZ. One patient died from acute respiratory failure during the study period.

Conclusions: Phenotyping of patients with serum A1AT 57 - 99 mg/dL at our institution is inadequate. Accordingly, regular continuous medical educational programs on A1AT phenotyping targeting healthcare providers are warranted.

Keywords: Alpha-1 antitrypsin deficiency; Serine proteinases; Aging; Smoking; Emphysema; Cirrhosis

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Introduction

Alpha-1 antitrypsin deficiency (A1ATD) disease is manifested by low (< 100 mg/dL; 11 mmol/L) serum levels leading to multi-organ injury, including pulmonary emphysema and chronic liver disease [1, 2]. The diagnosis of A1ATD requires two-step laboratory testing, determination of serum alpha-1 antitrypsin (A1AT) level and phenotyping if A1AT < 100 mg/dL (< 20 µmol/L) [2]. In clinical practice, however, routine determination of serum A1AT level followed, as indicated, by phenotyping in patients with pulmonary emphysema and/or chronic liver disease remains low despite availability of both assays in clinical laboratories [3-7].

To that end, delayed diagnosis of A1AT heterozygosity in the presence of serum A1AT < 100 mg/dL, the threshold level below which A1ATD is diagnosed [2], in patients with pulmonary emphysema and/or chronic liver disease may predispose them to accelerated decline in lung or liver function if their ongoing exposures to environmental toxicants, such as tobacco smoking, dust, and alcohol, are not curtailed [8-14]. To that end, the COPDGene Study found that PiMZ heterozygous non-Hispanic Whites and African Americans in the USA who smoke are at increased risk for pulmonary emphysema compared with Z allele non-carriers (PiMM or PiMS) [15]. In addition, genetic counseling of offsprings of PiMZ patients may be considered [1, 2, 16].

To begin to address this issue, we determined whether A1AT phenotyping is performed in patients with serum A1AT 57 - 99 mg/dL seen at our institution.

Materials and Methods

Patients

We reviewed the medical records of patients seen at the Jesse Brown VA Medical Center (JBVAMC) in Chicago, Illinois

Table 1. Patient Characteristics

Demographics	Phenotype performed (n = 13)	No phenotype performed (n = 17)	P value
Age (years)	61 (19)	51 (17)	0.145
Male, n (%)	12 (92)	15 (88)	0.719
Body mass index (kg/m^2)	28.6 (6.4)	29.2 (4.7)	0.783
African Americans, n (%)	7 (54)	7 (41)	0.478
Hispanics, n (%)	1 (8)	3 (18)	0.43
Whites, n (%)	5 (38)	7 (41)	0.865
Alpha-1 antitrypsin (mg/dL)	77.6 (5.7)	91.6 (9.2)	0.009
Hypertension, n (%)	5	2	0.189
Diabetes mellitus, n (%)	3	2	0.678
Heart disease, n (%)	5	2	0.189
Current or former smoker, n (%)	9 (69)	8 (47)	0.23
Chronic lung disease, n (%)	9 (69)	5 (29)	0.063
Chronic liver disease, n (%)	3 (23)	11 (65)	0.033
Chronic lung and liver disease, n (%)	1 (8)	1 (6)	-
Pulmonary function tests			
FEV_1 (L)	2.7 (1.5)	2.2 (1.1)	0.474
FEV_1 % predicted	70 (18)	61 (22)	0.38
DL_{CO} (mL/min/mm Hg)	21 (10.5)	14.7 (8.5)	0.308
DL_{CO} % predicted	68 (27)	54 (30.3)	0.375

Data are expressed as means ± standard deviation (SD) where appropriate. FEV_1: forced expiratory volume in 1 s; DL_{CO}: diffusing capacity of the lungs for carbon monoxide.

from January 1, 2019, to October 21, 2022, with reported serum A1AT 57 - 99 mg/dL by nephelometry and phenotyped by isoelectric focusing performed by Quest Diagnostics, Secaucus, NJ, USA [2]. The JBVAMC is a teaching hospital with 200 acute care beds in Chicago, Illinois that provides a full range of health services, including pulmonary medicine, for 62,000 Veterans residing in metropolitan Chicago and northwest Indiana with state-of-the-art medical technology as well as education and research. The medical center is affiliated with the University of Illinois College of Medicine in Chicago, Northwestern University Feinberg School of Medicine, and University of Chicago Pritzker School of Medicine.

In each case, pertinent demographic, clinical, and pulmonary function tests data were extracted. Patients with physician-diagnosed chronic obstructive pulmonary disease (COPD), asthma or bronchiectasis were considered to have chronic lung disease. Patients with physician-diagnosed hepatitis, cirrhosis or persistent elevations of serum transaminases were considered to have chronic liver disease.

Statistical and data analyses

Data are presented as means and standard deviation (SD) where appropriate. Due to the relatively small sample size, appropriate statistical tests were chosen to compare between groups. Continuous data were compared using Student's *t*-test, while categorical data were analyzed using Fisher's exact test. $P < 0.05$ was considered statistically significant.

Institutional Review Board approval/ethical compliance

The JBVAMC Institutional Review Board has designated this study as quality improvement not subject to human subjects research regulations.

Results

Thirty patients (90% males; age, 60 ± 18 years (mean ± SD)) with A1ATD were identified (Table 1). Fourteen were African Americans, four Hispanics, and 12 non-Hispanic Whites. The majority were current or ex-smokers. Fourteen (47%) patients had lung disease, 14 (47%) patients had liver disease, and one patient had both lung and liver diseases. Mean ± SD forced expiratory volume in 1 s (FEV_1) and lung diffusing capacity were 2.57 ± 1.41 L (67±19% predicted) and 18.7 ± 10 mL/min/mm Hg (64±28% predicted), respectively. Only 13 patients (43%) underwent phenotype testing, seven were African Americans, five Caucasians, and one Hispanic. Pulmonologists ordered eight tests, hepatologists three and primary care providers two. Six patients had MZ phenotype, four MS, and three SZ. One patient died from acute respiratory failure during the study period. Pulmonologists ordered phenotyping on 75% and 85%

of MS and MZ phenotypes, respectively, while hepatologists ordered phenotyping on all patients with SZ phenotype. Healthcare providers other than pulmonologists or hepatologists ordered nine A1AT tests in 17 patients with circulating A1AT < 100 mg/dL and no phenotype (53%). Moreover, only 10 patients with circulating A1AT < 100 mg/dL without phenotyping were referred to pulmonologists or hepatologists for further evaluation. In addition, pulmonologists ordered A1AT phenotype tests in 10 out of 13 patients with lung disease. By contrast, A1AT phenotyping was not performed in 11 out of 14 patients with liver disease (P = 0.033) (Table 1). We found no documentation in the medical records indicating that genetic counseling was recommended for or provided to family members of all patients.

Discussion

The results of this study show that phenotyping of patients with serum A1AT 57 - 99 mg/dL seen at our institution was performed in less than half of the cases. The reason(s) underlying these phenomena was not addressed in this study. We postulate that it may be related, in part, to the unfamiliarity of practitioners with current A1AT testing guidelines [2]. Whether similar observations are reported by other institutions is uncertain. To the best of our knowledge, however, no previous studies have reported inadequate A1AT phenotyping in predominantly African Americans and Hispanic patients with serum A1AT 57 - 99 mg/dL. Taken together, we propose that regular continuous medical educational programs about A1AT phenotyping targeting practitioners are warranted.

Taliercio et al [5] found that A1ATD is overlooked by internal medicine house officer and respiratory therapists at the Cleveland Clinic main campus hospital. The investigators attributed this finding, in part, to poor knowledge of A1ATD among these healthcare providers. In addition, Greulich et al [4] found that internists and general practitioners in Germany and Italy have low awareness of A1ATD. Similar observations were reported from Spain and Portugal [6, 7]. Collectively, these studies inform the need to establish training programs for healthcare providers about A1AT testing of at-risk individuals.

Several limitations of our project are notable. It is a retrospective, single site study involving a relatively small number of predominantly African American males. In each case, no molecular genetic testing of A1AT was documented in the electronic medical records [3, 10, 15]. Although a considerable proportion of our patients were presented with isolated chronic liver disease, the possible contribution of serum A1AT 57 - 99 mg/dL to this condition was not addressed in 78% (11/14) of subjects [9, 12, 13]. Given our sample demographics, the S and Z alleles are thought to have first emerged in Northern and Iberian European populations, and consequently their prevalences in African-American populations are rarer still [1]. Despite these limitations, we propose that a larger, prospective, multi-site study should be performed to support or refute our initial observations.

In summary, we found that phenotyping of patients with serum A1AT 57 - 99 mg/dL seen at our institution was performed in less than half of the cases. We propose that regular continuous medical educational programs about A1AT phenotyping targeting healthcare providers are warranted.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Documentation of a waiver of informed consent was obtained from the Jesse Brown VA Medical Center Institutional Review Board.

Author Contributions

ZZE contributed to conceptualization, methodology, data curation, formal analysis, writing and editing the original and revised manuscript and project administration. NT contributed to data curation, formal analysis, writing and editing the original and revised manuscript. MW contributed to data curation, formal analysis, writing and editing the original and revised manuscript. IR contributed to conceptualization, methodology, data curation, formal analysis, writing and editing the original and revised manuscript, and project supervision.

Data Availability

Deidentified data can be accessed upon written request and approval from the corresponding author.

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