CHEST

Original Research

COPD

Spirometric and Gas Transfer Discordance in α_1-Antitrypsin Deficiency

Patient Characteristics and Progression

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Background: **Phenotypic differences in physiologic, radiologic, and clinical characteristics are increasingly recognized in COPD. The factors associated with α_1-antitrypsin deficiency (A1AD) physiologic phenotypes and how they progress with time have yet to be explained.**
Methods: **The study comprised 530 patients with the homozygote Z variant (PiZZ) A1AD; 255 patients had ≥ 3 years of data for longitudinal analysis. Patients were categorized into four groups using lower limits of normal for the carbon monoxide transfer coefficient (Kco) and postbronchodilator FEV_1/FVC ratio. Group comparisons were undertaken for demographic, clinical, physiologic, health status, survival, and CT scan data.**
Results: **Groups with normal lung function or isolated gas transfer defect had the lowest smoking history, least emphysema, and best health status. The group with airflow obstruction (AO) alone had a greater smoking history, more emphysema, and worse health status compared with the normal group. The group with combined AO and gas transfer defect was the worst. The group with AO alone had a faster subsequent decline in Kco than the normal group ($P = .002$) and the group with both AO and reduced gas transfer ($P < .001$) and was more likely to change groups with time (62% moved to group B). Lower baseline Kco and male sex predicted 89% of the movement to the group with both physiologic abnormalities.**
Conclusions: **There are distinct physiologic phenotypes in A1AD with differing demographic features that relate to progression.** ***CHEST 2014; 145(6):1316–1324***

Abbreviations: A1AD = α_1-antitrypsin deficiency; AO = airflow obstruction; Kco = carbon monoxide transfer coefficient; LZ910 = lower-zone density of −910 Hounsfield units; PFT = pulmonary function test; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SR = standardized residual; TLC = total lung capacity; UZ910 = upper-zone density of −910 Hounsfield units; VI = voxel index

COPD is a group of conditions characterized by irreversible airflow obstruction (AO). There is increasing awareness of phenotypic differences in physiologic, radiologic, and clinical characteristics that occur in varying proportions in this heterogeneous disease. These phenotypes may reflect different underlying pathologic processes, contrasting prognoses, and management strategies. Identifying phenotypes will improve the understanding of COPD and may facilitate specific management regimens. Valid phenotypes should provide prognostic information and have predictive value for the patient[1] with support from mortality analysis.

α_1-Antitrypsin deficiency (A1AD) is the most recognized genetic susceptibility factor for COPD. It is an autosomal codominant disorder that affects around one in 2,000 whites in Northern Europe and predisposes the development of early-onset emphysema.[2] The most common, clinically relevant deficiency type is the homozygote Z variant (PiZZ), associated with a critically low serum concentration of α_1-antitrypsin and, classically, basal pan acinar emphysema.

Previous studies from our group have related A1AD phenotypes to emphysema distribution and physiology. Parr et al[3] showed that the carbon monoxide transfer coefficient (Kco) related better to upper-zone emphysema and FEV_1 to lower-zone emphysema. Holme and Stockley[4] explored this by assessing a small number of age-matched patients with isolated FEV_1 or Kco abnormality defined as < 80% predicted for age and sex. The data confirmed that isolated FEV_1 abnormality linked with a more basal emphysema distribution and isolated Kco abnormality with a more apical distribution. However, the small number of

subjects precluded determining whether the patterns change with time and any demographic association. The aim of the current study was to explore factors that might predict or be associated with physiologic phenotypes and to assess progression over time to determine whether or how these phenotypes might change.

Materials and Methods

The first 530 patients with PiZZ and complete baseline data to 2008 who attended the Antitrypsin Deficiency Assessment and Program for Treatment (ADAPT) project were included in a cross-sectional study. The longitudinal study included 255 patients with at least 3 years of follow-up (four data points). Patients were reviewed at least 6 weeks after any exacerbation and underwent full pulmonary function tests (PFTs) using British Thoracic Society and the Association of Respiratory Technicians and Physiologists guidelines,[5] blood gas sampling, quantitative CT imaging (where possible), health status assessment (St. George's Respiratory Questionnaire [SGRQ]), and breathlessness assessment (modified Medical Research Council dyspnea score). For a subgroup of patients, mean exacerbation frequency per year was defined using the Anthonisen criteria.[6] Although subjects were entered into the ADAPT project at differing stages of their disease, their survival was defined from the date of their first PFTs until the censor date of January 7, 2012, or date of death if that occurred earlier. The South Birmingham Ethics Committee approved this study (LREC No. 3359), and written informed consent was obtained from all patients.

Spirometry was measured pre- and postnebulized salbutamol (5 mg) and ipratropium bromide (500 μg) treatment using a wedge bellows spirometer (CareFusion Corp), lung volume was measured by body plethysmography, and gas transfer was measured using the single-breath carbon monoxide method.[7] Predicted values were determined using Miller regression equations[8] except for lung volumes, for which the European Community of Coal and Steel equations[9] were used. Abnormality of physiologic data was determined using the standardized residual (SR) to define the lower limit of normal (−1.645 SR) as recommended by American Thoracic Society and European Respiratory Society[10]: SR values = (observed result − predicted result)/residual SD for the prediction equation.[11] Reversibility was defined as >200 mL and >12% increase defined from the predicted FEV_1.[12,13]

High-resolution CT scan was available for 92% of the patients (n = 489). All scans were assessed by experienced radiologists, and emphysema was noted using recognized criteria.[14] For 300 of the patients, this was undertaken in our department using a protocol to determine the voxel index (VI) at a density threshold of −910 Hounsfield units at the level of the inferior pulmonary veins for the lower zones (lower-zone density of −910 Hounsfield units [LZ910]) and the level of the aortic arch for upper zones (upper-zone density of −910 Hounsfield units [UZ910]), as described previously.[3]

Subjects were classified into physiologic groups using the lower limit of normal for postbronchodilator FEV_1/FVC and Kco (Fig 1). The group with normal FEV_1/FVC and Kco was labeled N; the group with both tests returning abnormal results was labeled B; the group with abnormal FEV_1/FVC alone was labeled F; and the group with abnormal Kco alone was labeled K. Index cases refer to patients identified following presentation with symptoms, and nonindex cases refer to individuals identified through family screening.

Statistical analysis was performed using PASW Statistics, v.18 (IBM). Nonparametric data were compared using the Mann-Whitney *U* test and a *t* test for parametric data. The Pearson χ^2 test was used to compare distribution of data between groups. A *P* value ≤ .05 was accepted as significant with Bonferroni correction for multiple comparisons. Changes in FEV_1 and Kco were calculated for the patients with ≥ 3 yearly annual follow-up using linear regression. Multivariate logistic regression analysis was performed to identify variables that predicted movement between subgroups.

Results

Demographic details of the 530 subjects are shown in Tables 1 and 2. The distribution of baseline FEV_1/FVC SR and Kco SR for each subject is illustrated in Figure 2.

The FEV_1/FVC SR for the cohort had a bimodal distribution (Fig 3), while Kco was normally distributed. Groups N and K (normal FEV_1/FVC results) were grouped together and compared with groups F and B (abnormal FEV_1/FVC results). Those with abnormal FEV_1/FVC results had a greater smoking history than those in whom the results were normal (median pack-years, 18.00; interquartile ranges, 7.20-27.00, 0.00, and 0.00-8.00, respectively; $P < .001$), included a higher proportion of ever smokers and fewer never smokers (86% vs 46% and 14% vs 54%, respectively; $P < .001$), consisted of more men (63% vs 37%, $P < .001$) and more index cases (88% vs 31%, $P < .001$), were older (mean age [± SEM], 51.7 ± 0.46 vs 44.1 ± 1.59; $P < .001$), and had more basal emphysema assessed as the ratio of LZ910 to UZ910 VI (13.88 ± 0.86 vs 2.25 ± 1.08, respectively; $P < .001$).

Variables That Characterize Each Physiologic Phenotype

Group N: These patients had PFT findings in the normal range (Table 3), including PaO_2. The majority (64.4%) of the patients were women, which is an overrepresentation of the UK population (51% women[15]) and also higher than in groups F ($P = .046$) and B ($P < .001$) (Table 4).

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