CHEST

Original Research

GENETIC AND DEVELOPMENTAL DISORDERS

Differences in the Pattern of Structural Abnormalities on CT Scan in Patients With Cystic Fibrosis and Pancreatic Sufficiency or Insufficiency

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Background: **Cystic fibrosis (CF) genotypes characterized by pancreatic sufficiency (PS) are generally associated with milder disease vs genotypes characterized by pancreatic insufficiency (PI); however, the correlation between pancreatic status and type and severity of structural lung changes has not been studied. We aimed to evaluate differences in the severity and distribution of pulmonary manifestations of CF in patients with PS vs PI.**

Methods: **We retrospectively evaluated changes in individual lobes and the whole lung on chest CT scan with the modified Brody score. The study population included 84 (39 female, 45 male) patients with CF aged 4 to 68 years (mean, 20.5) treated from 2000 to 2010. Our institutional review board waived the requirement for informed consent. The severity of lung changes and distribution of pulmonary disease were compared by Student *t* test, nonparametric Pearson χ^2 test, or mixed-design analysis of variance for 28 patients with CF-PS and 56 with CF-PI. Correlations were evaluated with the Pearson (continuous variables) or Spearman ρ (nonparametric variables) tests. A linear regression model was used for multivariate analyses.**

Results: **Compared with patients with CF-PS, those with CF-PI had more-severe lung disease (*P* = .001) with predominant upper lobe involvement (*P* = .002) and significant differences in Brody scores for bronchiectasis and bronchial wall thickening. Lung manifestations in patients with CF-PS did not show predominant involvement of any one area (*P* = .133).**

Conclusions: **In patients with CF-PI, structural lung changes are more severe with upper lobe predominance, prominent bronchiectasis, and bronchial wall thickening vs lower severity and more general distribution of changes in those with CF-PS.** ***CHEST 2013; 144(1):208–214***

Abbreviations: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; HRCT = high-resolution CT; PI = pancreatic insufficiency; PS = pancreatic sufficiency; TBS = total Brody score

Cystic fibrosis (CF) is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene that result in the absence or dysfunction of the CFTR protein, which regulates ion transport across the apical membrane of certain epithelia. In the lungs, CFTR dysfunction leads to airway surface liquid depletion and adherence of thickened and viscous mucus to airway surfaces. The result is decreased mucociliary clearance and impaired host defenses. Dehydrated, thickened secretions lead to endobronchial infection and an exaggerated inflammatory response, resulting in the development of bronchiectasis and progressive obstructive airways disease. Despite increasing

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longevity in patients with CF, progressive pulmonary damage causes significant morbidity, and > 90% of mortality in this patient population results from pulmonary complications.

Pulmonary function is variable in patients with CF.[1-4] Spirometry measures, evaluated through FEV_1 in absolute values and compared with a reference population (FEV_1 % predicted), are regarded as the gold standard for assessing severity of CF lung disease and for gauging prognosis.[5] Reduced FEV_1 in patients with CF has been well described in the literature. However, despite extensive research into genotype and phenotype relationships, the association between lung disease, expressed as a reduction in FEV_1, and genotype has not been established apart from rare mutations that are associated with milder lung disease.[6,7]

CT scanning of the chest, particularly high-resolution CT (HRCT) scanning, has gained importance for grading the severity of lung disease and monitoring its progression and for guiding clinical management and intervention.[8-11] Cross-sectional studies of children with CF demonstrated that HRCT scans are more sensitive than traditional pulmonary function tests in detecting early signs of lung disease.[12-14] HRCT scan studies in patients with CF demonstrate bronchiectasis, bronchial wall thickening, mucous plugging, consolidation, cysts, ground glass opacities, and air trapping. Several scoring systems that estimate pulmonary disease by CT scanning have proven to be reliable.[15-18] HRCT scanning has also been shown to be more sensitive to intercurrent changes in lung disease compared with pulmonary function tests.[10,19,20]

Most patients with CF experience pancreatic insufficiency (PI), with impaired or absent pancreatic enzyme excretion leading to fat malabsorption, whereas about 15% have adequate pancreatic function to maintain normal nutrition (pancreatic sufficiency [PS]) and do not require pancreatic enzyme supplementation. In CF, pancreatic function has been shown to correlate with genotype, and PS genotypes are associated with milder disease.[9,21,22] Compared with patients with PI, those with PS usually are given a diagnosis later and have lower sweat chloride levels, better nutritional status, and longer life expectancy.[23]

To our knowledge, no study has analyzed the correlation between pancreatic status as defined by genotype and the type and severity of structural lung changes in CF. The aim of this study was to correlate the pattern and distribution of structural lung disease as demonstrated on HRCT scan in patients with CF-PI vs those with CF-PS.

Materials and Methods

This study included patients with CF treated at the Center for Chronic Diseases of Childhood of the Hebrew University Hadassah Medical Center between January 1, 2000, and December 31, 2010. These patients had genetic testing, HRCT scan examinations, routine pulmonary function tests at the time of CT scan, and pancreatic function evaluation as part of their clinical assessment during stable periods of their disease. Digital medical records and imaging files were evaluated retrospectively for patients who met inclusion criteria. The study was approved by our institutional review board, and written informed consent was waived (Committee on Research Involving Human Subjects of Hebrew University Hadassah Medical School, 0324-08-HMO).

The diagnosis of CF was made according to criteria established by a Cystic Fibrosis Foundation consensus panel.[24] Pancreatic function was defined in all patients on the basis of 3-day stool fat collection and fecal elastase assessment. *Pseudomonas* colonization was diagnosed from three positive sputum cultures over the year prior to the chest CT scan. Oral glucose tolerance testing was used in the diagnosis of CF-related diabetes mellitus (blood glucose levels > 200 mg/dL at 2 h). All patients with CF-related diabetes mellitus were treated with insulin. Patients with glucose intolerance were not included. FEV_1 % predicted and FVC were assessed according to American Thoracic Society/European Respiratory Society guidelines.[25]

HRCT scans were performed with a dual-slice CT scanner (Twin Flash; Marconi Medical Systems Israel Ltd), a four-slice multidetector spiral CT scanner (LightSpeed Plus; GE Healthcare), or a 16-slice CT scanner (LightSpeed; GE Healthcare). Images were acquired using standard scan parameters, including a maximum 120 kVp, auto mA (maximum, 350 mA), a pitch of 1, and a 512×512 matrix. Slice width was 3.75 to 5 mm for conventional scans and 1 to 1.25 mm for high-resolution images, which were reconstructed with a bone algorithm. All chest CT scans were obtained in a single breath-hold during suspended end inspiration, in supine position, without contrast material.

CT studies were jointly reevaluated on lung and mediastinal windows using our institutional picture archive and communication system (Centricity PACS; GE Healthcare) by one experienced pediatric radiologist (N. S.) and one experienced chest radiologist (N. H.) who were blinded to the patients' pancreatic function status. In patients who had more than one CT scan during the study period, only the last scan was evaluated.

Lung changes were assessed on high-resolution images in the lung window. For each lung lobe, including the lingula, which was counted as a separate lobe, the Brody score was calculated[15] with a slight modification: Hyperaeration of the lungs was evaluated instead of air trapping because expiratory images were not obtained in all patients. Such modification of the Brody score has been used previously.[26,27] Briefly, subscores for the presence and severity of bronchiectasis, mucous plugging, bronchial wall thickening, parenchyma, and focal hyperaeration in each lobe were calculated. Parenchymal findings of ground glass opacities, consolidations, and cysts or bullae were considered in determining a single parenchyma subscore.[15] The sum of subscores comprised the lung total Brody score (TBS) for each patient.

Statistical Analysis

TBS and scores for each lung lobe are presented for the PI and PS groups as descriptive statistics and percentiles. Continuous data are expressed as mean ± SD, unless otherwise specified. We hypothesized that structural lung changes expressed as a Brody score would correlate with clinical phenotype; other analyses were exploratory. Groups were compared by two-tailed independent Student *t* test or the nonparametric Pearson χ^2 test as appropriate. Within-subject comparisons among the upper, middle, and lower lobes were conducted by mixed-design analysis of variance. Normality of the distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Analysis of covariance was used to