How abnormal is the normal? Clinical characteristics of CF patients with normal FEV1

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Abstract

Background Normal values (>80%) of Forced Expiratory Volume in one second (FEV1) in patients with Cystic fibrosis (CF) may lead to the interpretation that there is no lung disease. This study is a comprehensive analysis of lung involvement in CF patients having normal FEV1. Methods Patients were recruited from two CF Centers: Hadassah Medical Center, Jerusalem and Vall d' Hebron Hospital, Barcelona. Lung disease was assessed by lung clearance index (LCI), chest CT-Brody Score, respiratory cultures, number of pulmonary exacerbations (PEx) and days of antibiotic treatment in the year prior to the assessment. Results Of the 247 patients, 89 (36%) had FEV1 [?]80% and were included in the study (mean age 17.6 range 4.25-49 years). Chronic P. aeruginosa infection was found in 21%, and 31% had at least one major PEx in the year prior to the study. Abnormally elevated LCI was found in 86% of patients, ranging between 7.52-18.97, and total Brody score (TBS) was abnormal in 92% (range 5.0-96.5). Patients with chronic P. aeruginosa had significantly higher LCI (p=0.01) and TBS (p=0.01) which were associated with more major PEx (p = 0.04 and p<0.001, respectively) and more days of intravenous (IV) antibiotic treatment in the preceding year (p=0.03 and p=0.002, respectively). Conclusions Most CF patients with normal FEV1 have already physiological and structural lung abnormalities which were associated with more PEx and IV antibiotic treatment.

Introduction

The life expectancy and quality of life of patients with Cystic fibrosis (CF) have greatly increased over the last decades. Early diagnosis, preventive treatment, prompt and aggressive management of pulmonary exacerbations (PEx) and complications, and treatment with CFTR modulators have led to improved outcome[1,2]. However, lung disease continues to be the major cause of morbidity and mortality in CF[1,3].

Forced expiratory volume in 1 second (FEV_1), measured by spirometry, is considered the gold standard for disease severity in CF. It is being used routinely to monitor lung disease status, to determine the need for lung transplantation, to measure the response to therapies and as an outcome measure in clinical trials[4,5]. Lung disease severity is commonly categorized according to FEV_1 %predicted and is considered *normal* at> 80% predicted. Therefore, FEV_1measurements over time serve as a guide for physicians, patients, parents and caregivers in the management of the disease and as indicator for treatment intensity. Normal FEV_1 may be falsely interpreted as having lungs that are free of disease, and may influence treatment recommendations and adherence.

Studies, mainly of preschool and young children, have demonstrated that the lung clearance index (LCI) may be abnormal in patients with mild lung disease according to FEV_1[6-9]. Other studies on small numbers of young patients, with normal pulmonary function, demonstrated abnormalities in chest CT. To the best

of our knowledge, there is no comprehensive evaluation of lung disease severity for patients above early childhood, who have normal pulmonary function measured by FEV_1.

The aim of this study was to perform a broad assessment of the extent of lung disease in patients with CF with FEV_1>80% of all age groups, as determined by clinical, physiological and structural characteristics of CF disease severity.

Methods

The study was approved by both hospital IRB-committees and informed consent was obtained from the patients or parents/caregivers. The study was conducted between 2015 – 2018. Patients above the age of 4 years with a confirmed diagnosis of CF[10], FEV_1 [?]80% predicted, clinically stable, and with no pulmonary exacerbations (PEx) in the four weeks prior to the study, were recruited from two CF Centers, the Hadassah Medical Center in Jerusalem, Israel, and the Vall d' Hebron Hospital in Barcelona, Spain.

Demographic data e.g., age, gender, CFTR-mutations, body mass index (BMI), pancreatic status [pancreatic insufficiency (PI) or sufficiency (PS)] and the presence of CF-related diabetes (CFRD), were obtained from patient files. Spirometry was measured according to ATS/ERS guidelines[11]. FEV_1 results were transformed into Z-scores using the Global Lung Function Initiative calculator (version 3.3.1). Multiple breath washout (MBW) test was performed using the Exhalyzer D (EcoMedics AG, Duernten, Switzerland), according to ERS/ATS Consensus Guidelines[12], and was carried out on the same visit day of the spirometry in order to correlate the results. Mean LCI calculated from a minimum of two technically valid and repeatable tests was reported. Analysis of MBW data was performed using the nitrogen washout FRC/LCI software (Spiroware).

All chest high resolution computed tomography (HRCT) scans performed during the study period (up to one year before or after spirometry and LCI tests) were examined by an experienced radiologist or by a specifically trained pediatric pulmonologist. HRCT scans were analyzed based on the modified Brody score; hyperaeration of the lungs was assessed instead of air trapping as expiratory images were not available for all patients[13]. 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 parenchymal subscore. The sum of subscores comprised the lung Total Brody Score (TBS) for each patient, ranging from 0 to 207. Pulmonary exacerbations (PEx) were defined as acute clinical deterioration, including malaise, anorexia, dyspnea, fever, increased cough, change in sputum quantity/quality, worsening in nutritional status and/or decline in pulmonary function, requiring addition or change of oral (PO) or intravenous (IV) antibiotics (Abx). Pulmonary exacerbations were subdivided into *minor* exacerbations, requiring PO antibiotics and*major* exacerbations, if IV Abx had to be initiated. Expectorated or induced sputum samples for microbiologic analysis are routinely collected from CF patients at each visit to the CF Center. Respective data were retrieved from patient files and/or electronic medical records. Chronic *P. aeruginosa* (PA) infection was defined by the Leeds criteria, i.e. >50% of the sputum samples over the preceding 12 months were positive[14]. Chronic PA infection, the number and type of PEx and duration of Abx treatment in days, during the previous year, were evaluated for each spirometry, LCI and HRCT test time point performed by each patient. A six-minute walk test (6MWT) was performed according to ATS guidelines[15]. The 6MWT results (i.e. six-minute walk distance [6MWD]) were transformed into Z-scores based on reference data[16,17] using the following formula: {value found - normal value / standard deviation}.

Statistical analysis

Data are reported as mean and standard deviations (SD). Pearson's correlation analysis was used to determine correlations between LCI and FEV_1, Brody scores, BMI and Z-6MWD, as calculated by the Minitab version 19.0.

Associations between LCI and CFTR mutations, pancreatic status, chronic PA infection, and the number of major and minor PEx were evaluated by assessing the differences between LCI means using paired T-tests. $P < 0.05$ was considered statistically significant.

Results

Of the 247 patients followed at the two centers, 89 patients (36%) had FEV_1 [?]80% predicted measured at 147 different time points and data was available for all the study parameters. Table 1 summarizes the CFTR mutation classes of the participating patients, showing that most of them have 2 mutations from class I, II and/or III mutations, which are associated with the classical more severe phenotype and PI, and 11 patients (12%) have CFRD.

Almost all the patients with normal pulmonary function demonstrated the presence of lung disease: 86% had elevated LCI, 92% had structural abnormalities measured by CT-Brody score, 21% have chronic PA infections, 19% had at least one major PEx requiring IV antibiotic treatment during the year previous to the assesment.

As shown in Figure 1, 86% of patients have abnormal LCI (LCI >7.5) values, some of which were even substantially increased. A correlation between LCI and FEV_1 could be observed even in the normal range, though the correlation was not strong (Figure 1). Analyzing the different ages of the patients, we noticed that FEV_1 as well as LCI were found to be weakly correlated to the patient age (r=-0.18; p=0.03 and r=0.33; p<0.001, respectively).

Most of the patients had significant structural abnormalities in their lungs as seen on HRCT, and as can be seen in Figure 2, it had weak correlation with FEV_1 (r=-0.32; p=0.008).

The most common structural abnormalities observed were air trapping, increased peribronchial thickening, and bronchiectasis (in 83%, 78%, and 54% of the patients respectively) (Table 1). These three parameters were found to be strongly correlated with LCI (air trapping r=0.49; p<0.001; peribronchial thickening r=0.74; p<0.001, and bronchiectasis r=0.68; p<0.001). Furthermore, a high correlation between TBS and LCI was observed (r=0.77; p<0.001) (Figure 3). Patients with normal or slightly increased LCI were found to have minimal structural changes, whereas patients with high LCI had significant structural changes as expressed by high TBS.

Chronic PA infection was found in 19 patients (21%), and was significantly associated with older age (mean age 26.8±12.1 yrs of PA positive vs 14.5±5.5 yrs of PA negative, p<0.001). Patients with chronic PA infection had significantly higher LCI values compared with those with no PA (11.9 ± 3.1 vs. 9.7 ± 2.3 respectively, p=0.01) and significant higher TBS (38.3 ±25.0 vs. 20.2 ± 19.4 respectively, p=0.01). Furthermore, as shown in Table 2, the 28 patients who had at least one major PEx during the year previous to the study had significant higher LCI (p=0.04) and TBS (p<0.001) values. There were 13 patients who received more than 14 days of IV Abx treatment in the year prior to the study. These patients had significant higher LCI (p=0.03) and TBS values (p=0.002). No significant differences were found for FEV_1, LCI and/or TBS for the other variables analyzed, including gender, CFTR mutation classes, pancreatic status, BMI, CFRD, 6MWD test, number of minor PEx and/or number of PO Abx treatment days in the previous year.

Discussion

This study demonstrates that most patients with normal pulmonary function, measured by FEV_1, already have significant lung disease according to physiological (measured by LCI), structural (HRCT changes) and clinical (chronic PA and PEx) parameters. Furthermore, having high LCI and/or high CT scores was associated with chronic PA infection, increased number of major PEx and more days of IV antibiotic trreatment, all indicators of CF disease activity and predictors of subsequent FEV_1 decline.

It was shown in infants, diagnosed through newborn screening, that early pulmonary abnormalities can be identified already in the first years of life[18]. Furthermore, it has been shown previously that high LCI levels can be found in asymptomatic infants or small children[19-23]. In this study, different from most of the published studies, the majority of patients were teenagers and adults, and as it is known, in older patients FEV_1 is considered to best represent disease severity[5].

FEV_1 in the normal range may be interpreted as "normal lungs", which may lead to an erroneous misin-

terpretation of the severity of the disease, and can result in fewer treatments offered by the CF team, or decreased adherence to treatments by the patients. However, as shown in the current study, FEV_1 in the normal range, is not sensitive enough to identify early and even significant lung disease and therefore, it is important to follow specially patients with normal or slightly decreased FEV_1 regularly using other clinical parameters. Frequent monitoring of lung disease by LCI and chest CT, repeated sputum cultures with immediate eradication of newly acquired bacterial infections, and early treatment of PEx may prevent or at least postpone irreversible lung damage and disease progression.

Frequent monitoring of CF patients using chest CT scans does carry a potential risk due to radiation exposure and is therefore not always performed routinely. The new imaging technology with short duration of radiation exposure and the low radiation CF protocols are associated with minimal radiation. Furthermore, studies demonstrated that acute structural changes can be reversible when treated immediately[24-30]. The very strong correlation between LCI and Brody Score suggests that LCI can be used more frequently and as long as LCI levels remain normal, routine chest CT scans can be postponed to the time when levels of LCI become abnormal or deteriorate. It has been shown that in young children, inhalations with hypertonic saline[24] and treatment of pulmonary exacerbations[25] can improve LCI. Furthermore, CFTR modulator therapy was also shown to improve LCI levels[26], suggesting the interventions at this stage of lung disease can reverse abnormalities.

An important result of this study is the correlation between the clinical parameters of CF severity such as PA infection, PEx and days of IV antibiotic treatment with abnormal LCI and TBS values. Therefore, it is essential to early identify and treat all changes with the aim to prevent or reverse disease progression.

In conclusion, the importance of this study lays in the demonstration that regardless of their age, most CF patients with normal FEV_1 already have evidence of lung disease, as detected by LCI and chest CT scan, and is associated with increased PEx and more days of IV treatment. Additional studies are necessary to determine if early and aggressive treatments will preserve or reverse changes detected by LCI and CT scans and if early treatment with the current and future CFTR modulators will avoid or postpone early lung damage.

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