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Short Communication

Evidence of diminished FEV_1 and FVC in 6-year-olds followed in the European cystic fibrosis patient registry, 2007–2009

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Abstract

Background: Many infants with cystic fibrosis (CF) exhibit airway inflammation, gas trapping, bronchiectasis, and/or reduced flow, but by age 6 years have forced vital capacities (FVC) and expiratory volumes in 1 second (FEV_1) within the variability range of the normal population. We sought evidence of diminished FVC and FEV_1 in 6-year-olds with CF.
Methods: GLI 2012 FVC and FEV_1 Z-scores for 6-year-olds from the European CF Patient Registry were plotted against theoretical values from the Normal distribution.
Results: Mean FVC and FEV_1 Z-scores for 681 patients (322 females) were −0.43 (SD = 1.41) and −0.65 (1.40). Z-scores were consistently lower than expected for the normative population by quantile–quantile plot.
Conclusions: Diminished FEV_1, and to a lesser extent FVC, is found in a large majority of this population, consistent with an established body of evidence that loss of lung function begins early in life for most, if not all, children with CF.

Keywords: FEV1; Early disease progression; Epidemiology; Infants

1. Introduction

The advent of cystic fibrosis (CF) newborn screening has produced CF infant populations largely lacking respiratory signs and symptoms [1]. When asymptomatic infants with CF are studied by bronchoalveolar lavage, high-resolution computerized tomography (HRCT), and/or infant pulmonary function testing, large proportions have important markers of early CF lung disease such as elevated airway inflammation, gas trapping, bronchiectasis, and/or reduced flow [1–5]. However, a majority of 6-year-olds with CF have forced expiratory volumes in 1 second (FEV_1) and forced vital capacities (FVC) well within the bounds of normal variability of the unaffected population. The apparent paradox of widespread early lung disease in infants with CF but essentially 'normal' lung function in 6-year-olds as measured by FVC and FEV_1 creates a conundrum: are asymptomatic infants with CF appropriate candidates for chronic respiratory treatments targeted at lung disease progression or not? We have analyzed FEV_1 % predicted, FVC % predicted, and associated Z-scores for 6-year-olds followed at CF care centers in Europe for evidence that diminished lung function extends beyond the minority of children with CF with 'abnormally low' FVC and/or FEV_1 values and into the larger population with values within the normal range of variability for a healthy population.

2. Methods

Patients with CF included in this analysis were cared for in an ECFS member country that had supplied FEV_1 and FVC data to the European CF Registry for each year from 2007 to 2009. Only countries that had agreed to contribute patient data

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to this specific analysis were included. Patients were required to have FEV_1 and FVC measures (liters) and accompanying height (cm), age (years), and sex available between their 6th and 7th birthdays.

Global Lung Function Initiative (GLI) 2012 FEV_1 % predicted, FVC % predicted, FEV_1/FVC, and associated Z-scores were determined for each patient using Microsoft Excel 2007 and a macro downloaded from http://www.lungfunction.org [6]. Patient race, which is not tracked in the ECFS Patient Registry, was assumed to be Caucasian. Observed Z-score distributions for the study population were plotted against the Normal distribution and observed Z-scores were plotted against theoretical Z scores derived from the Normal distribution in quantile–quantile plots.

3. Results

A total of 681 patients (322 females, 359 males) from Austria, Belgium, Czech Republic, Germany, Denmark, France, Greece, Hungary, Israel, Italy, The Netherlands, Portugal, and Slovenia were included in analyses. In all, 51.1% of 6-year-old CF patients followed in their respective National Patient Registries between 2007 and 2009 had required data available and were included. Slightly more patients were included from 2007 (253) than from 2008 (215) and 2009 (211) (Table 1) due to a steadily decreasing availability of complete records (54.4%, 50.3%, and 48.4%) over the period.

The mean FEV_1 for the study population was 91.6 ± 17.9% predicted (±SD), corresponding to a mean Z score of −0.65 ± 1.40 (Table 1). Mean FEV_1 Z-scores were not different for females (−0.65 ± 1.42) and males (−0.64 ± 1.39), but varied by year: −0.66 ± 1.37 for 2007, −0.75 ± 1.42 for 2008, and −0.53 ± 1.43 for 2009 (Table 1), with the increase observed between 2007 and 2009 not statistically significant (P = 0.32). The mean FEV_1/FVC ratio for the population was 0.87 ± 0.09, corresponding to a mean Z-score of −0.36 ± 1.36. In all, 151 patients (22.2%) had FEV_1 Z-scores < −1.645, the lower limit of normal (LLN), more than four times as many as the 34 patients (5%) anticipated if the population followed the Normal distribution (Fig. 1). The mean FVC Z-score was −0.43 ± 1.41 (Table 1), with 118 patients (17.2%) having FVC Z-scores below the LLN (Fig. 1).

Distributions of FVC and FEV_1 Z scores by sex were comparable, with FEV_1 Z-scores tending to be lower than FVC Z-scores (Table 1, Fig. 1). When analyzed by quantile–quantile plot, Z-scores for both FVC and FEV_1 were consistently lower than would have been anticipated from random sampling of 'healthy' populations (Fig. 2).

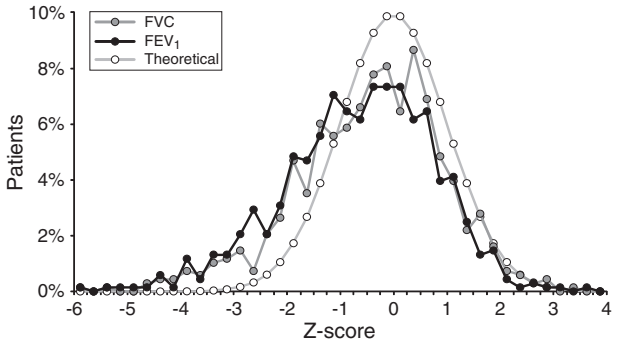

Fig. 1. Distributions of FVC and FEV_1 Z-scores and theoretical Z-scores among 681 6–year-olds followed in the ECFS Registry between 2007 and 2009. Gray circles represent FVC Z-scores, black circles represent FEV_1 Z-scores, and open circles represent theoretical Z-scores derived from the Normal distribution.

4. Discussion

FEV_1 % predicted is commonly used to stratify CF lung disease stage in children old enough to reliably perform spirometry [7]. This has proven to be useful, as FEV_1 % predicted has been shown to be a significant risk factor for morbidity [8] and mortality [9] and a surrogate for demonstration of efficacy for chronic CF respiratory therapies [10]. However, it has been demonstrated that FEV_1 is a relatively insensitive measure of early CF lung disease (with FVC less sensitive still) [11], as the incidence of abnormal findings by HRCT or multiple breath washout far exceed those by spirometry among school age children with CF [12].

An unfortunate and unintended consequence of using FEV_1 % predicted to stratify CF lung disease stage is that some CF clinicians might mistakenly conclude that a majority of the 77.8% of 6-year-olds with CF and FEV_1 Z-scores above the LLN in our study had no evidence of lung disease, and thus warranted observation but not necessarily intervention. However, quantile–quantile plots (Fig. 2) suggest that both FVC and FEV_1 Z-scores of almost our *entire* population of 6-year-olds with CF were shifted to lower values, a result that would suggest that most, if not all, of these children already had diminished FVC and FEV_1 and had experienced some level of CF lung disease. In addition, evidence of modest obstruction in

Table 1
Study population characteristics by year and sex.

	2007 Cohort (N = 253)	2008 Cohort (N = 217)	2009 Cohort (N = 211)	Female Cohort (N = 322)	Male Cohort (N = 359)	All (N = 681)
Females, N (%)	122 (48.2%)	111 (51.2%)	89 (42.2%)	–	–	322 (47.3%)
Mean age, yrs (SD)	6.34 (0.25)	6.31 (0.24)	6.34 (0.25)	6.33 (0.24)	6.34 (0.25)	6.33 (0.25)
Mean FEV_1 % predicted (SD)	91.5 (17.5)	90.4 (18.0)	93.1 (18.2)	91.6 (18.0)	91.7 (17.8)	91.6 (17.9)
Mean FEV_1 Z-score (SD)	−0.66 (1.37)	−0.75 (1.42)	−0.53 (1.43)	−0.65 (1.42)	−0.64 (1.39)	−0.65 (1.40)
Mean FVC % predicted (SD)	94.7 (17.6)	93.6 (17.6)	95.8 (18.3)	94.7 (17.7)	94.7 (18.0)	94.7 (17.8)
Mean FVC Z-score (SD)	−0.43 (1.40)	−0.51 (1.39)	−0.34 (1.45)	−0.44 (1.40)	−0.42 (1.42)	−0.43 (1.41)

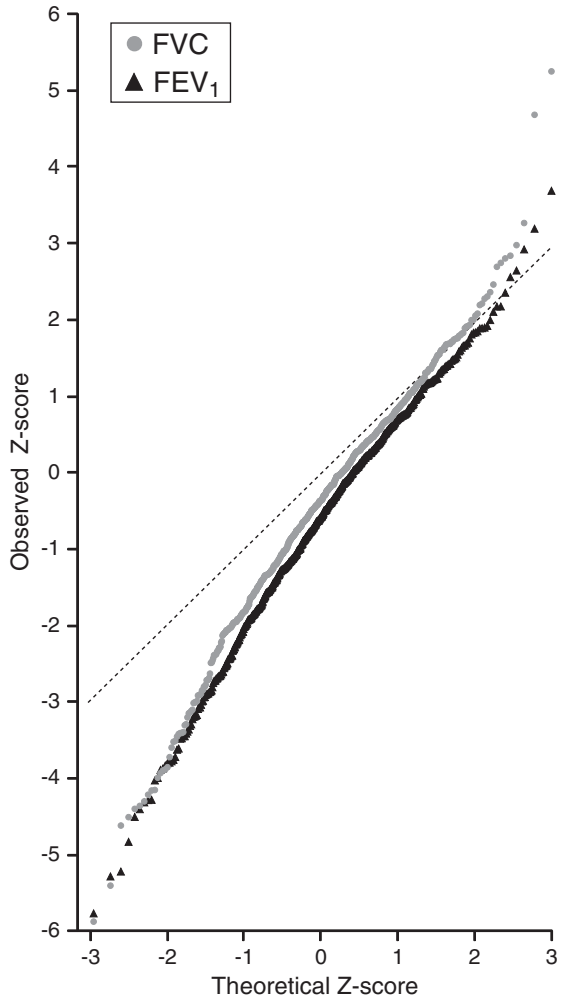

Fig. 2. Quantile–quantile plot of observed FVC and FEV_1 Z-scores among 681 6–year-olds followed in the ECFS Patient Registry between 2007 and 2009 by theoretical Z-scores derived from the Normal distribution. Gray circles represent FVC Z-scores and black triangles represent FEV_1 Z-scores. Dashes mark line of identity.

the population was suggested by a mean FEV_1/FVC Z-score of −0.36. This interpretation is consistent with the previously reported prevalence of risk factors in early childhood that have been associated with diminished FEV_1 at age 6 years [13], as well as previous observations that markers of early lung disease such as inflammation, gas trapping, and reduced flow are relatively common in CF infants [1–5]. Further, longitudinal studies have confirmed that reduced flow in infants with CF persists through school age [14], that reduced FEV_1 in school-age children is predicted by ventilation inhomogeneity in younger children with CF [15], and that small airway disease can be detected by forced expiratory flow at 75% of FVC (FEF_{75}) before substantial changes in FEV_1 are observed in young children with CF [11].

Our analysis was limited by an inability to analyze FVC and FEV_1 Z-scores for all 6-year-olds with CF in the countries studied due to incomplete data availability, and we cannot unequivocally state that inclusion of all 6-year-olds would not have affected our results. FEF_{75} Z-score distributions, which were not available for these patients, would have been useful to confirm our observations of a general shift to worse spirometric measures. In addition, use of GLI 2012 normative equations may be an imperfect substitute for case-controlled studies of spirometry Z-scores of 6-year-olds in specific geographic regions. However, we feel that our general conclusion, that an FVC or FEV_1 within the normal range of variability is insufficient to establish that a 6-year-old child with CF has not already experienced diminished lung function, is unaffected by these limitations.

Our observations suggest that respiratory interventions intended to preserve lung function should not be limited to infants with CF who displays signs and symptoms of lung disease and 6-year-olds with 'abnormal' FVC and/or FEV_1, but rather should be considered more universally to improve outcomes. Analyses using quantile–quantile plots of FVC and FEV_1 Z-scores in school-age children with CF may prove useful in the future in evaluating the success of earlier intervention efforts.

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