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Original Article

Bronchiectases at early chest computed tomography in children with cystic fibrosis are associated with increased risk of subsequent pulmonary exacerbations and chronic pseudomonas infection

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Abstract

Background: Children with cystic fibrosis (CF) are often *Pseudomonas aeruginosa* (PsA) free and exhibit normal spirometry between the ages of 5 and 7. It is reported that computed tomography (CT) is more sensitive than FEV1 as an instrument in the identification of pulmonary disease. It is not known whether CF-CT scores in childhood may be used to highlight children at risk of developing severe disease.
Aims: 1 — To assess the number of respiratory exacerbations (RTEs) during a follow-up period of 6 years and their correlation with the CF-CT scores in young CF children. 2 — To assess whether PsA-negative CF children with high chest CF-CT scores are more likely to develop chronic PsA lung infection.
Methods: 68 chest CT performed in patients without chronic PsA infection were scored. All patients (median age 7.8 years) had at least 4 clinical, functional and microbiologic assessments/year in the subsequent 6 years. RTE was defined as hospitalization and IV antibiotic treatment for respiratory symptoms.
Results: 86.8% patients had <3 RTEs in the 6 year follow-up period. The number of RTEs in the 6 years subsequent to the CT scan was correlated to the bronchiectasis CT score (BCTS) ($r = 0.612$; $p < 0.001$) and to FEV1 at baseline ($r = -0.495$, $p < 0.001$). A BCTS ≥ 17.5 identified patients with >3 RTEs during follow-up (sensitivity: 100%, specificity: 85%), while FEV1 did not. Only BCTS was significant in a logistic multivariate model (RR 1.15). BCTS was significantly lower and FEV1 higher in patients who did not develop chronic PsA infection by the end of the study.
Conclusion: In CF children free from chronic PsA, both CT scores and FEV1 values demonstrate significant correlation with disease severity in the subsequent 6 years but CT score has higher predictive value in the identification of patients at risk.

Keywords: Cystic fibrosis; Computed tomography; Respiratory exacerbations; *Pseudomonas aeruginosa*

1. Introduction

Cystic fibrosis (CF) lung disease is progressive and characterized by the development of bronchiectasis and regional air trapping, chronic lower-airway bacterial infection, respiratory tract exacerbations (RTEs) and progressive decrease in lung function. Traditionally, spirometry (i.e. forced expiratory volume in 1 s or FEV1) has been used to monitor disease progression.

Recent data show that chest CT can help us identify structural abnormalities in children who are too young to perform routine spirometry that gives reliable values [1–3].

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Despite some concerns about ionizing radiation exposure and other disadvantages, for example its high cost, chest CT has become the gold standard for the diagnosis of bronchiectasis in CF and non-CF individuals [4,5]. The role of chest CT in monitoring the progression of CF lung disease has been extensively studied in the last few years, thanks to standardization of quantitative CF scoring systems [6]. A comparison between the CF-CT score, which is an upgraded version of the Brody CT scoring system, and other surrogate clinical endpoints in CF [7–9] shows that the high sensitivity of the bronchiectasis subscore is of more utility in diagnosis and tracking of early lung disease compared to FEV1 [2,10].

Longitudinal studies are needed to establish whether early-age CF-CT scores identify those patients who will then develop severe lung disease during adolescence or young adulthood.

Disease progression in CF is related to RTEs and chronic lung *Pseudomonas aeruginosa* (PsA) infection [11]. RTE is an accepted outcome in CF [12,13], although there is no consensus on its definition [14]. Up to this date however only two studies [7,15] have examined the correlation between chest CT scores and later RTEs in these patients; the follow-up period in both was 2 years. In addition, it is not clear whether the presence of bronchiectasis precedes PsA infection and thus whether it is an early determinant of lung disease progression.

The first aim of our study was to examine the association between chest CT scores and RTE over a longer period to establish whether they can identify those patients who are at risk of deteriorating. To our knowledge, there are no studies which describe the correlation between chest CT scores and RTEs over an extended follow-up in children with CF who are PsA free.

The second aim of our study was to investigate, in the cohort of young PsA-negative CF patients, whether CT scores and FEV1 could be used to identify those patients who are more likely to develop chronic PsA infection before adolescence. We investigated the abovementioned associations in a cohort of patients who all had 6 years of clinical, functional and microbiological follow-up after the first chest CT.

2. Methods

2.1. Study population

This retrospective analysis includes all eligible patients with a confirmed diagnosis of CF who had a chest CT scan during the period from January 2004 to April 2007 and who were subsequently followed in the Verona CF Regional Centre (Italy). Since 2004, starting from when they can reliably do pulmonary function tests, all of our patients have a routine chest CT scan every 2 to 3 years. We included only those CT scans performed as part of an annual check up when patients were clinically stable.

Eligible children 1) were aged ≥ 4 and ≤ 11 years, 2) had been diagnosed with CF (sweat chloride ≥ 60 mmol/l and/or two known CF mutations), and 3) were monitored for 6 years in our center, with at least quarterly clinical, spirometric and microbiological assessments every year throughout the period. We excluded: 1) patients for whom we had incomplete follow-up data and 2) patients who had a lung transplant before the end of the follow-up. The hospital review board approved the study protocol, and parents' written informed consent was obtained.

2.2. Follow-up assessments

Patients were seen every three months and assessed according to the European CF Society Standards of Care [16]. Clinical data were extracted from electronic patient records.

2.3. Chest CT scans

A single 4-detector row CT scanner (Somatom Plus 4, Siemens, Berlin, Germany) was used. The CT scans were obtained in the supine position using the following scan parameters: 80–120 kVp, 15–24 mAs, pitch of 1, with automatic tube current modulation. The lung parenchyma was evaluated using the following HRCT reconstruction parameters: 1 mm slice thickness at 3 to 10 mm intervals from apex to base during voluntary end inspiration breath-holds in cooperative patients. The calculated Dose Length Product or DLP range (DLP = volume CTDI * scan length) for the CT scans was 22–113 mGy * cm (estimated mSv range: 0.34–1.74).

2.4. CT scoring

All CTs were scored using a CF-CT scoring system (Brody II), proposed by Brody and colleagues [6]. Bronchiectasis, mucus plugging, airway wall thickening and parenchyma scores were calculated for each patient; air trapping was not evaluated. The maximum total CT score (243) is the sum of maximum values for each parameter (bronchiectasis, mucus plugging, airway wall thickening, opacities, air trapping) for every single lung lobe, considering the lingula as a separate lobe. Excluding air trapping, the maximum theoretical value is 216. For statistical analysis, only partial subscores were considered and expressed as a percentage of the maximum possible score (0–100).

All 73 scans were anonymized, randomized and scored using a modified Brody score [6] by two suitably qualified, independent observers (S.V. and M.L.). Mean CT scores were used for analysis.

2.5. Spirometry, respiratory cultures and exacerbations

All spirometry measurements were obtained using a single water bell spirometer (Biomedin, Padova, Italy). Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and forced expiratory flow between 25 and 75% of FVC (FEF 25–75) were expressed as percentages of predicted values and as Z scores. Reference equations for children by Zapletal and Samanek [17] were used.

Deep throat or sputum cultures were obtained at least every three months. The prevalence of PsA infection was assessed