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Original Research Article

A Hospital Based Comparative Study to Evaluate the Role of Computed Tomographic (CT) Scores and Pulmonary Function Tests to Detect Changes in Lung Disease in Children and Adults Diagnosed with Cystic Fibrosis (CF)

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Abstract:

Aim: The aim of the present study was to compare the ability of computed tomographic (CT) scores and pulmonary function tests to detect changes in lung disease in children and adults with cystic fibrosis (CF).

Methods: The present study was conducted in the Upgraded Department of pediatrics for one year. CT scans were available for 100 patients with CF (50 children and 50 adults). Patients were diagnosed as having CF when they had a positive sweat chloride test and/or two known CF mutations. The cohort was divided into subjects aged (less than years at first scan (children) and those aged above 18 years.

Results: In the present study, male was higher in both the groups. In children, 6 had pancreatic status as sufficient and 12 had sufficient pancreatic status as sufficient in adults. Interestingly, FEV1 worsened by 0.07 Z score in the children (p=0.03) and FEV1/FVC worsened by almost 0.1 Z score per year in both children (p=0.002) and adults (p=0.02). MEF25 and MEF50 also worsened in children (p=0.005 and 0.006, respectively) and adults (p=0.007 and 0.005, respectively), and RV worsened in adults (p=0.01). All other PFTs remained unchanged (p.0.07). Composite CT scores and all component CT scores except the mosaic perfusion score in children and adults and peripheral mucus plugging score in adults deteriorated significantly over time in children (p,0.004) and adults (p,0.03). There was no significant difference in the slopes for any of the parameters between children and adults (p.0.09), but the composite CT score and RV tended to deteriorate faster in adults than in children.

Conclusion: In conclusion, this study showed that routine CT scans deteriorated while PFTs remained unchanged or deteriorated at a slower rate in both adults and children with CF. The deterioration on the CT scan was best reflected in the peripheral bronchiectasis CT score in children and in both the composite CT score and peripheral bronchiectasis CT score in adults.

Keywords: Computed Tomographic, Pulmonary Function Tests, Cystic Fibrosis.

Introduction

With a greater proportion of children with cystic fibrosis (CF) having normal pulmonary function test (PFTs) [1] and very gradual decreases in FEV1 [2], it has become difficult or impossible to use FEV1 to identify those children at risk for more rapid lung disease progression. This is especially true in light of the study by Konstan and colleagues, which determined that the greatest risk factor for FEV1 decline in children with CF was having an FEV1 % predicted less than 100%. [3] Cross-sectional studies of children with CF have demonstrated that high-resolution chest computed tomography (CT) scans are more sensitive than traditional PFTs in detecting early signs of lung disease. [4-6] Additionally, chest CT scan has been shown to be more sensitive to intercurrent changes in lung disease than PFTs. [7-9] Given the sensitivity of chest CT scan in detecting early lung disease, chest CT scans may provide a tool for

predicting future lung disease progression. In a recent study, Loeve and colleagues demonstrated that chest CT scans scored using the Brody scoring system [4] could predict the frequency of pulmonary exacerbation over the ensuing 2 years, independent of FEV1 severity. [10] Having more frequent pulmonary exacerbations is associated with subsequent FEV1 decline. [3,11]

Magnetic resonance imaging (MRI) of the chest is becoming more available and popular in the detection and monitoring of early changes in lung structure and function, as well as routine follow-up care in people with cystic fibrosis (CF). [12-14] This radiation-free technique seems particularly feasible for children and adolescents who are much more prone than adults to the adverse effects of radiation. MRI can be successfully performed without sedation in most children aged 5 to 7 years and some even as young as 3 years. [15] In the absence of morphological changes, lung parenchyma shows normal perfusion, while damaged lung segments show impaired perfusion. [16] In addition to radiological studies in order to assess pulmonary disease in CF, researchers and clinicians utilize pulmonary function tests (PFT). Due to the progress in the standard care in CF, increasing numbers of affected individuals have normal spirometry [17] and in this group of patients, the multiple breath washout technique (MBW) is a more sensitive technique. [18] MBW, however, seems to perform sub-optimally in investigating the treatment response as well as in monitoring patients with more severe lung disease. [19] There also remains a group of patients with normal PFT results in whom lung disease might already be present. [20]

The aim of the present study was to compare the ability of computed tomographic (CT) scores and pulmonary function tests to detect changes in lung disease in children and adults with cystic fibrosis (CF).

Materials and Methods

The present study was conducted in the Upgraded Department of pediatrics, Patna Medical College and Hospital, Patna, Bihar, India for one year . CT scans were available for 100 patients with CF (50 children and 50 adults). Patients were diagnosed as having CF when they had a positive sweat chloride test and/or two known CF mutations. The cohort was divided into subjects aged less than 18 years at first scan (children) and those aged above 18 years. Pancreatic status and the prevalence of chronic Pseudomonas aeruginosa infection were assessed at the time of the first CT scan. Chronic Pseudomonas infection was defined as sputum or nasopharyngeal cultures positive for Pseudomonas on two or more occasions in 6 months. In all subjects' cultures had been obtained at an average interval of 1 month.

Lung Structure

Lung structure was evaluated using CT scans. In children, a single detector CT scanner (Philips LX, Philips Medical Systems, Best, The Netherlands) was used from 1997 to 1999, and a multidetector row (four or eight rows of detectors) CT scanner after 1999 (General Electric Light Speed Ultra, GE Medical Systems, Milwaukee, WI, USA). Scans were obtained using a beam current of 120 mA, an exposure time of 0.5 s, and a beam potential of 120 kV from lung apex to base at 15 mm intervals using 1.25 mm thick slices. In adults, a PQ 6000 scanner (Picker International Inc, Highland Heights, OH, USA) was used throughout the study period. Scans were obtained using a beam current of 160 mA, a 1 second exposure time, and a beam potential of 120 kV from lung apex to lung base at 10 mm intervals using 1.5 mm thick slices.

All scans were reconstructed with a high spatial frequency algorithm (bone), printed (window width 1400 Hounsfield units (HU), window level 2400 HU), blinded to date and patient identification, and scored in random order by two independent experienced observers using an adapted scoring system recently developed by Brody et al. [8] This scoring system evaluates the five lung lobes and the lingual as a sixth lobe for severity and extent of central and peripheral bronchiectasis, extent of central and peripheral mucous plugging, severity and extent of central and peripheral airway wall thickening, extent of opacities (atelectasis or consolidations), and extent of cysts and bullae. Hyperinflation (gas trapping) was excluded from scoring since not all scans had expiratory images and mosaic perfusion was scored instead. Ground glass pattern was not scored in this study. The maximum composite CT score without air trapping and ground glass pattern and with mosaic perfusion was 180.13 In addition, component CT scores were calculated by adding the component scores from the six lobes. Maximal component scores for central bronchiectasis, peripheral bronchiectasis, central mucus, peripheral mucus, central airway wall thickening, peripheral airway wall thickening, opacities, mosaic perfusion, and cysts or bullae were 18. For statistical analysis the mean composite and component CT scores of both observers were expressed on a scale of 0–100 (percentage of maximum possible score).

Lung Function

Conventional PFTs were done using a dry rolling seal spirometer (Master Lab, Jaeger, Wu¨rzburg, Germany). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), mid expiratory flow at 25% and 50% of VC (MEF25 and MEF50), residual volume (RV), and total lung capacity (TLC) were expressed as percentage of predicted values and as Z scores. The ratio between FEV1 and FVC and between RV and TLC was

calculated and expressed as a percentage, as percentage predicted, and as a Z score. For children, prediction equations developed by Quanjer and colleagues [21] were used for FEV1 and FVC and prediction equations developed by Zapletal and colleagues [22] were used for MEF25, MEF50, RV, and TLC. For adults, prediction equations from the European Respiratory Society [23,24] were used for all parameters. Spirometric tests (FEV1, FVC, MEF25 and MEF50) were performed in all patients at each annual checkup.

Results

Table 1: Baseline characteristics of study patients

	Children	Adults
Age (years)	12±4	27±3
Sex (M/F)	28/22	26/24
Pancreatic status (sufficient/insufficient)	6/44	12/38
Chronic Pseudomonas infection (yes/no)	10/40	15/35
FVC (% predicted)	97 (18)	94 (19)
FEV1 (% predicted)	97 (21)	78 (24)
RV (% predicted)	98 (42)	126 (47)
TLC (% predicted)	95 (18)	102 (12)
MEF50 (% predicted)	96 (34)	51 (30)
MEF25 (% predicted)	84 (46)	41 (33)
FEV1/FVC (%)	88 (9)	70 (13)
FEV1/FVC (% predicted)	98 (10)	84 (16)
RV/TLC (%)	26 (11)	33 (13)
RV/TLC (% predicted)	104 (43)	120 (42)
Composite CT score (points, %)	9 (11)	17 (13)

In the present study, male was higher in both the groups. In children, 6 had pancreatic status as sufficient and 12 had sufficient pancreatic status as sufficient in adults.

Table 2: Annual changes in pulmonary function test (PFT) results and composite and component CT scores in children and adults

Function	Children	Adult	p-value
FVC (Z score)	20.0006 (0.031)	0.0051 (0.032)	0.89
FEV1 (Z score)	20.0734 (0.029)	20.0397 (0.031)	0.47
RV (Z score)	0.0105 (0.035)	0.1025 (0.037)	0.09
TLC (Z score)	20.0028 (0.020)	0.0294 (0.021)	0.28
MEF50 (10log % pred)	20.0119 (0.0039)	20.0159 (0.0053)	0.53
MEF25 (10log % pred)	20.0133 (0.0045)	20.0155 (0.0051)	0.75
FEV1/FVC (Z score)	20.0944 (0.026)	20.0748 (0.030)	0.63
RV/TLC (Z score)	0.0231 (0.046)	0.0763 (0.041)	0.39
Structure (%) Composite CT score	1.007 (0.21)	1.547 (0.24)	0.09
Central bronchiectasis	1.253 (0.052)	0.978 (0.078)	0.60
Peripheral bronchiectasis	1.721 (0.049)	1.521 (0.065)	0.66
Peripheral mucous plugging	0.652 (0.036)	0.391 (0.038)	0.38
Central AWT	1.389 (0.060)	1.076 (0.067)	0.54
Peripheral AWT	0.931 (0.048)	0.807 (0.053)	0.76
Opacities	0.733 (0.039)	0.737 (0.043)	0.99
Mosaic glass pattern	20.354 (0.090)	0.264 (0.085)	0.38

Interestingly, FEV1 worsened by 0.07 Z score in the children (p=0.03) and FEV1/FVC worsened by almost 0.1 Z score per year in both children (p=0.002) and adults (p=0.02). MEF25 and MEF50 also worsened in children (p=0.005 and 0.006, respectively) and adults (p=0.007 and 0.005, respectively), and RV worsened in adults (p=0.01). All other PFTs remained unchanged (p.0.07). Composite CT scores and all component CT scores except the mosaic perfusion score in children and adults and peripheral mucous plugging score in adults deteriorated significantly over time in children (p,0.004) and adults (p,0.03). The strongest rate of deterioration was observed for peripheral bronchiectasis score in children (1.7% per year, p,0.0001) and for the composite CT score in adults (1.5% per year, p=0.0003). There was no significant difference in the slopes for any of the parameters between children and adults (p.0.09), but the composite CT score and RV tended to deteriorate faster in adults than in children.

Discussion

Patients with cystic fibrosis (CF) show progressive worsening in lung structure and function due to chronic infection and inflammation. [25-27]

Pulmonary function tests (PFTs) are considered the gold standard for monitoring changes in CF lung disease. [26] It has been found, however, that functional changes can be preceded by structural changes detected on computed tomography (CT) scans. [28,29] CT scoring systems can quantify structural abnormalities in CF in a reproducible fashion. [29 -32] A recent study in children from a single CF centre showed that structural lung abnormalities evaluated by composite CT scores worsened while PFTs remained stable or improved over a 2 year interval. In addition, the component CT scores for bronchiectasis and mucus plugging worsened significantly and irreversibly.

In the present study, male was higher in both the groups. In children, 6 had pancreatic status as sufficient and 12 had sufficient pancreatic status as sufficient in adults. Interestingly, FEV1 worsened by 0.07 Z score in the children (p=0.03) and FEV1/FVC worsened by almost 0.1 Z score per year in both children (p=0.002) and adults (p=0.02). MEF25 and MEF50 also worsened in children (p=0.005 and 0.006, respectively) and adults (p=0.007 and 0.005, respectively), and RV worsened in adults (p=0.01). All other PFTs remained unchanged (p.0.07). Composite CT scores and all component CT scores except the mosaic perfusion score in children and adults and peripheral mucous plugging score in adults deteriorated significantly over time in children (p,0.004) and adults (p,0.03). The strongest rate of deterioration was observed for peripheral bronchiectasis score in children (1.7% per year, p,0.0001) and for the composite CT score in adults (1.5% per year, p=0.0003). There was no significant difference in the slopes for any of the parameters between children and adults (p.0.09), but the composite CT score and RV tended to deteriorate faster in adults than in children. The fact that the peripheral bronchiectasis CT score declined faster than PFTs warrants further discussion. For several reasons we feel that the bronchiectasis CT score is an attractive outcome parameter, both clinically and in trials, and we believe this abnormality is most characteristic of CF lung disease. Evaluation of bronchiectasis on the CT scan is considered to be the gold standard [33-35] and PFTs are considered insensitive for diagnosing bronchiectasis. Bronchiectasis can be evaluated relatively easily on CT scans (as shown by the good interobserver agreement in this and other studies) [29] and, while it is argued that bronchiectasis is reversible in other diseases [36,37] in CF it is irreversible. Finally, we believe that airway wall thickening (related to airway inflammation), mucous plugging, and consolidations are all risk factors for the development of bronchiectasis, and bronchiectasis is therefore a highly relevant end stage feature of CF lung disease. We currently lack a true sensitive end point to monitor CF lung disease. Mortality and quality of life are considered true end points but they are insensitive. The relationship between bronchiectasis, CT score, and mortality remains to be investigated in CF but, from studies in patients with non-CF bronchiectasis, we know that the severity of bronchiectasis is closely correlated with quality of life. [38,39] It is likely that the same is true for CF although other factors such as pancreatic insufficiency and diabetes might obscure this correlation. Nevertheless, the sensitivity of this CT abnormality to track disease progression in CF is at present unknown and requires further study. In addition, we did not include potentially more sensitive PFTs such as multiple breath washout tests. The comparison between changes in such tests and CT parameters requires further study. The rate of progression of bronchiectasis could have been influenced by allergic bronchopulmonary aspergillosis (ABPA). The potential negative effect of radiation exposure of repeated CT scanning remains a point of discussion and concern. [40] When using repetitive CT scanning it is important to keep the cumulative lifelong radiation exposure as low as possible. For this reason, CT scans were performed once every 3 years rather than annually.

Conclusion

In conclusion, this study showed that routine CT scans deteriorated while PFTs remained unchanged or deteriorated at a slower rate in both adults and children with CF. The deterioration on the CT scan was best reflected in the peripheral bronchiectasis CT score in children and in both the composite CT score and peripheral bronchiectasis CT score in adults. Bronchiectasis can be scored reproducibly and is irreversible in CF. Our findings indicate that a composite CT score may be less useful than a peripheral bronchiectasis CT score since it consists of reversible and irreversible components, and not all components were scored reproducibly in this study. We conclude that, by providing complementary information to PFTs, the peripheral bronchiectasis CT score is important for monitoring CF patients clinically and is expected to become an important outcome parameter in clinical studies in CF.

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