ORIGINAL ARTICLE

# Cystic fibrosis in adults: clinical and spirometric aspects

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**Introduction: Cystic Fibrosis is usually diagnosed in childhood. In Brazil, few studies have addressed CF diagnosed in adulthood.**

**Objective: The aim of this study was to describe demographic and clinical characteristics and spirometric data of patients with CF diagnosed in adulthood (over 16 years of age) in Bahia, Brazil.**

**Methods: Twenty-eight patients with cystic fibrosis diagnosed in adulthood were evaluated at the Bahia State Reference Center for Cystic Fibrosis. Variables of interest were age, gender, race, body mass index (BMI), sputum culture, presence of sinusitis and bronchiectasis, spirometric tests with the best values performed for forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC) and response to bronchodilators.**

**Results: Mean age at diagnosis was 31.1 ± 12.4 years. Of the patients, 53.4% were black or mulatto and the mean body mass index was 18.7 ± 3.0 kg/m$^2$. *P aeruginosa* was present in 12 (43%) of the patients. The mean percentage ± SD of FVC and $FEV_1$ were 58.9 ± 21.6% and 44.1 ± 23%, respectively. In the group of patients testing positive for *P. aeruginosa* in sputum cultures, mean of the spirometry parameters were lower than those in the *P. aeruginosa*-free group. However, only the difference in FVC achieved a statistically significant difference (p = 0.0007).**

**Conclusions: In agreement with many authors, this study strengthen the point of view that CF must be investigated in patients with recurrent infections, sinusitis and bronchiectasis even in adulthood. Values of the percentages of FVC and FEV in relation to those foreseen were lower in patients who were *P. aeruginosa* hosts, suggesting greater deterioration of respiratory function.**

***Key words:*** **Cystic fibrosis/diagnosis. Adult. Spirometry/methods.**

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***Abbreviations used in this paper:***

**CF – Cystic fibrosis**
**BMI – Body mass index**
**FVC – Forced vital capacity**
**FEV1 – Forced expiratory volume in one second**
**SD – Standard deviation**

## INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutation in the cystic fibrosis transmembrane conductance regulator gene. More than 1400 mutations have already been reported by the Cystic Fibrosis Genetic Analysis Consortium.[1]

The incidence of CF ranges from 1/1200 to 1/400 in the Caucasian population and is considered rare in Asian and African populations.[2] In Brazil, there are no comprehensive epidemiological studies or neonatal screening programs that would provide an estimate of the incidence of the disease. It is estimated that more than 90% of cases go undiagnosed every year.[3]

A diagnosis of CF is made based on clinical manifestations and confirmation of high sweat chloride levels (chloride concentrations equal to or greater than 60 mEq/L).[4] The classic CF presentation is that of an obstructive suppurative pulmonary disease, and it may appear concurrently with exocrine pancreatic insufficiency or a history of CF within the family.[4] Approximately 90% of patients present with exocrine

pancreatic insufficiency.[4] Most male patients present with obstructive azoospermia.[4] The evolution of CF in patients presenting pancreatic sufficiency is milder, and such patients maintain better nutritional states and improved pulmonary function, often causing a delay in diagnosis.[5] The variability of phenotypic expression of CF depends on factors such as gene mutations, genetic load, and environmental factors.[2]

The aim of this study, carried out at the Cystic Fibrosis Reference Center of the State of Bahia, was to describe clinical findings, demographic characteristics and spirometric data obtained from 28 patients diagnosed with CF in adulthood (defined as older than 16 years of age). This is one of the few studies on CF in adults in Brazil and is even more relevant if we consider the fact that the population in Bahia is ethnically diverse, with a higher degree of miscegenation than in other parts of the country.

## METHODS

In this study, 110 patients diagnosed with CF in adulthood were identified. Of these 110, 28 (24.1%) were monitored from 1991 to 2001 at a reference center in Salvador, Bahia (Brazil).

The criteria used for the diagnosis of CF were those recommended by the Cystic Fibrosis Foundation in 1999, namely: one or more of the classical phenotypic characteristics or family history, together with sweat chloride levels higher than 60 mEq/L in sweat samples of at least 100 mg.[6] In all patients, 4 sweat samples were evaluated for chloride using the quantitative pilocarpine iontophoresis method.[7] Diagnoses of sinusitis or bronchiectasis were based on clinical and radiologic correlations.[8]

The demographic variables recorded were age, gender and race. Clinical conditions such as nutritional state and body mass index (BMI) were also noted. Spirometric measurements included forced vital capacity (FVC; percentage of predicted value) and forced expiratory volume in one second ($FEV_1$; percentage of predicted value), both prior to and after administration of a bronchodilator. In addition, at least 3 sputum culture samples were obtained on different occasions and submitted to microbiological testing for *P. aeruginosa*.

To evaluate nutritional states using BMI, patients that presented with a BMI < 18.5 $kg/m^2$ were considered nutritionally deficient. All patients were submitted to spirometric determination of FVC and $FEV_1$, both prior to and after the use of inhaled bronchodilator (fenoterol, 400 μg). A Vitalograph spirometer (Vitalograph, Buckingham, UK) was used in accordance with the criteria established by the American Thoracic Society (ATS).[9] The predictive values were calculated using the method described by Morris.[10] Residual volume was not evaluated.

Data were analyzed using SPSS statistical software, version 9.0. Quantitative variables are expressed as means ± standard deviation (SD), and qualitative variables are described in percentages. The Mann-Whitney test was used to estimate the statistical significance of differences between means. All statistical tests were bicaudal and a significance of 5% was considered significant.

## RESULTS

The mean age of the patients studied was 31.1 ± 13 years (median, 28.5; range, 17–67). Of the 28 patients, 15 (53.7%) were black or mulatto. Sixteen (60.7%) of the patients were female. The mean BMI was 18.7 ± 3.0 $kg/m^2$, and the mean sweat chloride level was 97.1 ± 16.8 mEq/L (range, 71.4–136 mEq/L). In 26 (93%) of the patients, there was digital clubbing and clinical as well as radiological evidence of sinusitis and bronchiectasis. All but one patient had a history of pulmonary disease in childhood. Only one patient was diagnosed with cor pulmonale. One patient was taking enzyme supplements due to celiac disease. Of the 11 male patients, 6 (54%) were submitted to sperm count and 4 (67%) presented with azoospermia. None of the 7 patients tested presented ΔF508 mutation.

The following infectious agents were identified in sputum cultures (3 samples per patient): *Pseudomonas aeruginosa* in 12 samples (43%); *Staphylococcus aureus* in 5 samples (18%); *Haemophilus influenzae* in 1 sample (3%), and saprophytic bacteria in 9 samples (30%). In 1 of the 5 samples in which *Staphylococcus aureus* was isolated, *Klebsiella pneumoniae* was also isolated.

Spirometric data are summarized in Table 1. Means ± SD of the percentages of predicted values for FVC and $FEV_1$ were 58.9 ± 21.9% and 44.1 ± 23.0%, respectively. There was positive response to the bronchodilator in 8 patients (28.8%). No statistically significant differences in functional parameter means were found in relation to race, gender or BMI. When we considered the patients colonized with *P. aeruginosa,* the mean of the percentage of the predicted value for FVC was significantly lower when compared to the mean of the value in noncolonized patients ($p = 0.007$). The mean of the percentage of the predicted value for $FEV_1$ was lower in the group colonized with *P. aeruginosa.* However, the difference between colonized and noncolonized patients was not statistically significant ($p = 0.092$).

## DISCUSSION

Typically, CF is diagnosed in childhood. About only 8% of patients are diagnosed after the age of 10.[11] In such patients, CF presents a less severe phenotypic expression.[11] The prevalence of CF is higher in Caucasians than in blacks. In the United States, the prevalence is 1:3,200 in Caucasians and 1:17,000 in blacks. The smaller proportion of Caucasians among the patients evaluated in the present series can be attributed to the fact that the population of the state of Salvador is predominantly (77.5%) black and mulatto.[13]

This is one of the few studies of Brazilian CF patients diagnosed in adulthood. Gan et al.[14] described a study of 143 patients with CF in which those diagnosed in adulthood (defined as older than 16 years of age) composed approximately 20% of the group. According to the authors, a delayed diagnosis is not necessarily the result of poor diagnostic methods. Rather, they postulated, it is the result of the distinct expression of a genotype within a group of patients presenting mild pulmonary disease and no gastrointestinal symptoms. It is possible that the patients in the present study, who are from a population with high levels of ethnic miscegenation (composed of descendants of African and Portuguese immigrants), may belong to a group of patients with a milder expression of the CF phenotype. We believe that the high proportion of late CF diagnoses in the present study (28/110; 24.1%) was related to a milder course of the disease during the early years of life, as well as to a lack of highly trained healthcare personnel able to diagnose and treat the disease. We would like to call the attention of physicians and pulmonologists to the fact that they should consider this diagnosis in adults, since the sweat test (for electrolytes) is inexpensive and easily performed.

In this study, the most common clinical manifestation was bronchorrhea (100%). The fact that only one patient needed enzyme supplements may represent a less pronounced expression of the phenotype in its gastrointestinal aspects. This milder type of manifestation has been described in patients with various ΔF508 mutations.[2] In a study of Caucasian patients in the southern and southeastern regions of Brazil, Raskin et al.[15] reported a 47.4% incidence of ΔF508 (the most common) mutation, a figure comparable to that seen in some Mediterranean peoples (namely Italians and Spaniards). This is not surprising, given that most people in those areas are of Italian or Spanish descent. The results of genotype studies in our cohort of patients may be in conflict with the findings of Raskin et al. In the southeastern Brazilian state of Minas Gerais, where ethnic miscegenation is at 50%,[16] the prevalence of ΔF508 mutation within the African-Brazilian population is 10.5%.[3] In the present study, 7 (25%) of the 28 patients were tested for ΔF508 mutations, and all 7 tested negative.

Spirometric results were compatible with moderate to severe obstructive lung disease. Even though residual volume was not measured, we can assume that the lower FVC values were due to airway obstruction and the consequent increase in residual volume.[17] When we compare the means of the percentages of the predicted values for FVC (58.9%) and for $FEV_1$ (44.1%) with those reported in American patients (80.9% for FVC and 68.9% for $FEV_1$),[11] we observe that the patients in our series presented more severe conditions. In their study of Dutch patients, Gan et al. demonstrated that spirometric results are lower in patients diagnosed with CF

before 16 years of age (FVC = 71.9% and $FEV_1$ = 52%) than in patients diagnosed later (FVC = 89.8% and $FEV_1$ = 72.5%). Both differences were statistically significant.[14] These results were also higher than those observed in the present study. These discrepancies may be due to sampling differences, especially those related to ethnicity, socioeconomic status, treatment procedures and age at time of diagnosis. These variables influence the evolution of CF, and environmental factors, number and severity of respiratory infections, genetic load, nutritional state, delay in seeking medical treatment or misdiagnosis may determine the differences in lung function parameters.[2]

A lower percentage of the predicted value for FVC ($p$ = 0.007) and a tendency toward lower percentages of the predicted value for $FEV_1$ ($p$ = 0.092) were observed in patients colonized with *P. aeruginosa*. Fritz-Simmons et al. demonstrated that patients colonized with *P. aeruginosa* presented lower values for FEV1 (64.5% of predicted) than did noncolonized patients (87.7%).[11] The findings of those authors are in contrast with those recorded in the present study, in which lower $FEV_1$ values were observed. Again, this can be attributed to differences in sample size, ethnicity and socioeconomic status between the two populations studied. In agreement with other data in the literature, the present study reinforces the idea that a diagnosis of CF must be considered for patients with recurrent pulmonary infections, sinusitis and bronchiectasis, even in adulthood. Spirometric values demonstrate more severe respiratory involvement in patients colonized with *P. aeruginosa*.

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TABLE 1
Spirometric parameters according to colonization with *Pseudomonas aeruginosa*

| Pulmonary function parameters | Total (n = 28) | Colonization with *P. aeruginosa* (n = 27)# | | |
|---|---|---|---|---|
| | | Yes (n=12) | No (n=15) | p* |
| **FVC (% of predicted value)** | | | | |
| Mean ± SD | 58.9 ± 21.6 | 44.1 ± 18.7 | 67.7 ± 18.2 | 0.007 |
| Variation | 21.0–92.0 | 21.0–84.0 | 35.0–92.0 | |
| **$FEV_1$ (% of predicted value)** | | | | |
| Mean ± SD | 44.1 ± 230 | 33.1 ± 13.8 | 50.1 ± 24.4 | 0.092 |
| Variation | 15.0–92.0 | 17.0–65.0 | 15.0–92.0 | |

FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second; *Mann-Whitney test; #Sputum sample cultures were obtained from all but one patient, who presented no expectoration.