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Cystic fibrosis at a Brazilian center of excellence: clinical and laboratory characteristics of 104 patients and their association with genotype and disease severity

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Abstract

Objective: To identify the clinical, laboratory and radiographic characteristics of the cystic fibrosis patients under care at Universidade Estadual de Campinas (UNICAMP) in the last decade of the twentieth century, and to investigate the association of these characteristics with genotype and severity of the disease as measured by the Shwachman score.

Methods: Descriptive, retrospective and cross-sectional study of the patients assisted at UNICAMP hospital's Cystic Fibrosis Clinic from July 1990 to July 2000.

Results: One hundred and four patients were studied; 53.8% male; 93.3% Caucasian; 89.4% presented with respiratory symptoms; 59.6% presented with digestive symptoms; 5.8% had meconium ileus; 4.8% had diabetes. The mean age at onset of symptoms was 3 months, and the mean age at diagnosis was 2 years and 4 months. At diagnosis, 69.9 and 56.6% of the patients had weight and height below 10th percentile, respectively; in 10.6%, sweat chloride was < 60 mEq/l. *Staphylococcus aureus* was found in 80.2%, *Pseudomonas aeruginosa* in 76.0%, and *Burkholderia cepacia* in 5.2%. ΔF508 homozygosis was observed in 18.75%, whereas 62.50% of the patients were ΔF508 heterozygous. A moderate/severe Shwachman score was found in 15.7%. Eighteen patients died in that period (17.3%). The mean age at death was 7 years and 8 months; median survival after diagnosis was 18 years and 4 months. Patients who have at least one ΔF508 mutation have more frequent alterations in fecal fat levels when compared to patients who do not have this mutation ($p < 0.05$). There were no differences in any parameter between ΔF508 homozygous and heterozygous patients.

Conclusions: The clinical and laboratory characteristics of the 104 patients studied were similar to the characteristics described for patients in other countries. Exceptions are the higher age at diagnosis and lower survival. Our results support the recommendation for early diagnosis and the need for more treatment opportunities in the population of cystic fibrosis patients.

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Introduction

Cystic fibrosis (CF) has been widely studied by many authors from several different countries, making possible greater understanding of its pathophysiology and the introduction of new therapeutic methods and impacting significantly with reduced morbidity and increased patient survival.

Little research exists, however, evaluating cystic fibrosis populations from developing countries. As a result the treatments and public health measures offered to patients with cystic fibrosis in such countries are based on international data and don't take their specific peculiarities into account. In addition to treating patients without real knowledge of their characteristics, this situation has further implications since, when it becomes necessary to choose which drugs will be offered by the state (as it is impossible to offer all of

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them) it is fundamental that this choice be based on the local population's characteristics.

The World Health Organization drew attention to this fact in 1997[1] making the following recommendations for actions to be taken at Cystic Fibrosis Services in developing countries: neonatal screening as a means of establishing incidence and identify those newborn babies affected; setting-up of genetic laboratories should be encouraged to identify CF genetic mutations, the development of diagnosis and treatment centers with multidisciplinary teams; the establishment of a national organization involving cystic fibrosis patients' family members, friend and other volunteers; the establishment of a national register; the dissemination of information on the condition to health professionals, public authorities and the general public and increased collaboration between the groups and other organizations (including the pharmaceutical industry).

This lack of information is observable in Brazil where little research has been done describing and analyzing the characteristics of patients with cystic fibrosis.

The objective of this study was to describe the clinical and laboratory characteristics of cystic fibrosis patients treated at the *Universidade Estadual de Campinas* (UNICAMP) hospital's Cystic Fibrosis Clinic, during the last decade of the twentieth century and check for associations with the ΔF508 mutation and disease severity, as measured by the Shwachman.

Patients and Methods

This was a retrospective, descriptive, cross-sectional cohort study of patients treated at the UNICAMP Cystic Fibrosis Clinic, between July 1990 and July 2000.

All patients who had attended at least one consultation at the Cystic Fibrosis Clinic and whose diagnosis had been confirmed by clinical history and at least two sweat tests returning chloride values greater than or equal to 60 mEq/l or by the identification of two mutations.

Electrolyte concentration in sweat was tested by means of sweat stimulation by iontophoresis with pilocarpine.[2]

Sputum cultures were taken to identify *Staphylococcus aureus*, *Pseudomonas aeruginosa,* Mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*. Samples were seeded in chocolate agar, blood agar, supplemented agar, MacConkey culture medium (*Pseudomonas* specific) and thioglycollate. Mucoid strains of *Pseudomonas aeruginosa* were visually identified by their characteristic morphology (presence of liquid mucus). Selective media were not employed for *Burkholderia cepacia.*

The following mutations were tested for: ΔF508, G542X, N1303K, G551D, R553X and W1282X. The ΔF508 mutation was detected by means of polymerase chain reaction (PCR) and analyzed on 8% polyacrylamide gels, using the modifications described by Rommens et al.[3] Other mutations were analyzed by the PCR technique in association with restriction enzyme digestion.

Descriptive analysis employed mean, median and standard deviation values for continual variables and absolute frequency for discrete variables. Categorical variables were analyzed using the chi-square test. Fisher's exact test was applied in cases when one of the cells in the 2 X 2 tables was less than or equal to 5. Continuous and sequential measurements were compared across the two groups using the Mann-Whitney test. Survival time was analyzed using the Kaplan-Meier method. Curves were compared through the application of the Wilcoxon (Breslow) test. The significance level adopted was 5%.

This research was approved by the UNICAMP Committee for Ethics in Research.

Results

One hundred and four patients were studied, of whom, 53.8% were male, 93.3% Caucasoid and 6.7% Negroid. Eighteen patients died during the period covered by the study. Parental consanguinity occurred in 6.2% of the population under study.

Respiratory and digestive symptoms occurred in 89.4 and 59.6% of the patients, respectively. Six had histories of *meconium ileus* and five developed *diabetes mellitus*.

The stated age of onset of symptoms varied from birth to 20 years, with a mean of 16 months and median of 3 months (Figure 1).

Age at diagnosis varied from the neonatal period to 29 years and 11 months, with a mean of 4 years and 2 months and median of 2 years and 4 months (Figure 2).

With respect of nutritional status, 69.9 and 56.6% of the patients exhibited weight and stature below the tenth percentile, respectively, at first consultation.

Room air transcutaneous hemoglobin oxygen saturation was above 95% in 59.5%, between 91 and 95% in 32.9% and below 91% in 7.6% of patients.

Sweat chloride concentration was below 60 mEq/l in 10.6% (11) of the patients, with 1.9% (2) exhibiting values below 40 mEq/l; 28.8% (30) of the patients presented values between 60 and 100 mEq/l and 60% (63) presented values above 100 mEq/l.

More than 80% had been colonized by *Staphylococcus aureus*, 76% by *Pseudomonas aeruginosa*, more than half by Mucoid *Pseudomonas aeruginosa* and 5.2% by *Burkholderia cepacia* (Table 1).

Spirometry was used for 55 patients and was normal in 27.3% (15), indicated restrictive respiratory disorder 18.2% (10), obstructive respiratory disorder 25.4% (14) and mixed respiratory disorder in 29.1% (16).

Ninety-six patients were analyzed genetically, of whom 18.75% (18) were homozygous for ΔF508 and 62.5% (60) were ΔF508 heterozygotes. This being so, 50% of the chromosomes studied exhibited the ΔF508 mutation.

The following percentages of other mutations were found in the 192 chromosomes studied: G542X (4.17%), N1303K (2.08%), G551D (1.04%), R553X (0.52%), W1282X (0.52%).

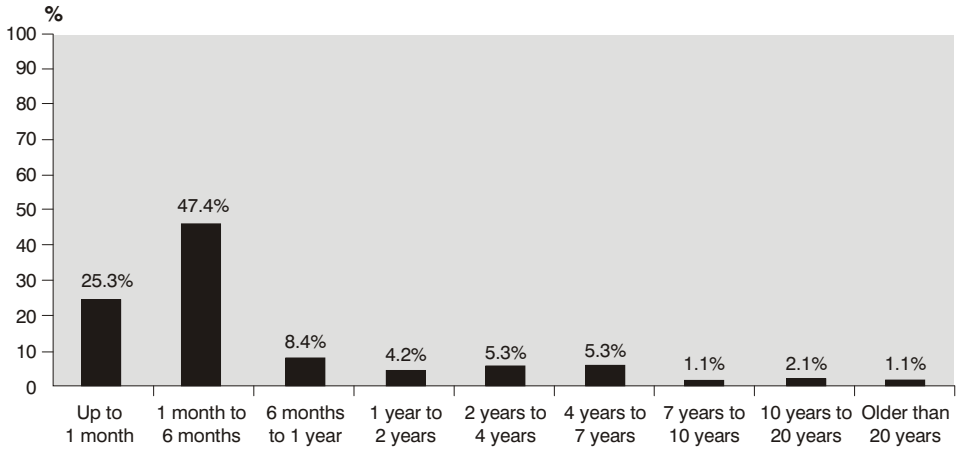

Figure 1 - Distribution of patients according to the age of onset of symptoms (n = 95)

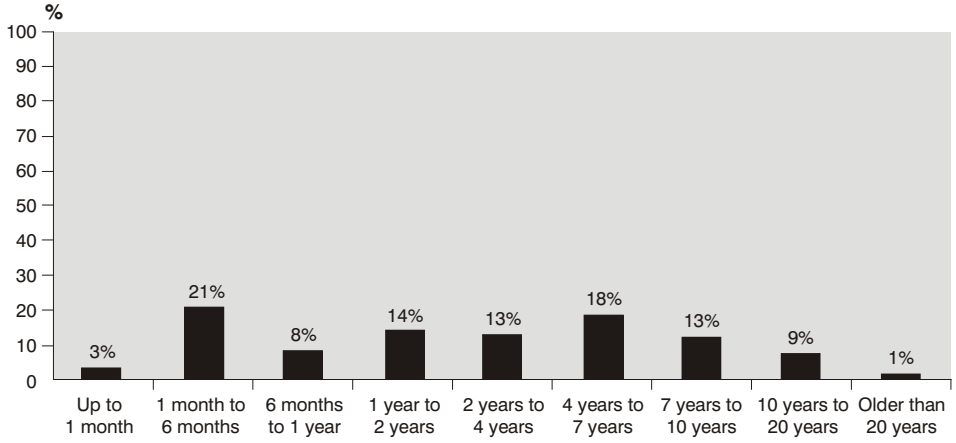

Figure 2 - Distribution of patients according to the age at diagnosis (n = 100)

The Shwachman score was calculated for 83 patients and returned: 57.8% (48) with an excellent or good score, 26.5% (22) with an average score and 15.7% (22) with a moderate or severe rating.

Table 1 - Distribution of patients according to the colonization by different bacteria (n = 96)

Colonization	%	n
Staphylococcus aureus	80.2	77
Pseudomonas aeruginosa	76.0	73
Pseudomonas aeruginosa mucosa	53.1	51
Burkholderia cepacia	5.2	5
P. aeruginosa and *P. aeruginosa* mucosa	51.0	49

During this period 18 patients (17.3%) died. Tem were male and eight female, 17 Caucasoids and one Negroid, all died from respiratory insufficiency.

Age at death varied from 6 months to 23 years and 1 month. Mean average age at death was 9 years and 5 months with a median of 7 years and 4 months.

At the point when the study was completed, median post-diagnosis survival was 18 years and 4 months and 81.39% of the patients had survived for 10 years after diagnosis. The post-diagnosis survival curve for the sample can be observed in Figure 3.

An attempt was made to test the correlation between the Shwachman score (SS) and the patients' clinical and laboratory characteristics. Eighty-three subjects were included in this analysis, of whom 54.2% (45) were male, 57.8% (48) presented an excellent or good SS, 26.5% (22) average and 15.7% (13) moderate or severe. Table 2 shows the statistical correlation of clinical and laboratory characteristics with the SS.

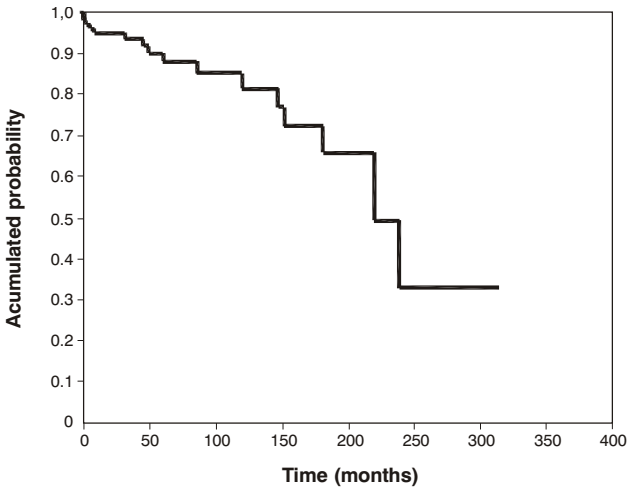

Figure 3 - The post-diagnosis survival curve for the sample analyzed using the Kaplan-Meier method

Clinical and laboratory differences between patients with cystic fibrosis with and without the ΔF508 mutation were analyzed. Ninety-six patients were studied, of whom 81% (78) had the ΔF508 mutation and 19% (18) did not present this mutation; 52% (50) were male. Table 3 presents the statistical correlation between clinical and laboratory parameters and the presence or absence of the ΔF508 mutation.

Seventy-eight patients were studied in order to evaluate the clinical and laboratory differences between patients with the ΔF508 mutation in the homozygote and heterozygote forms, of whom 23% (18) were homozygotes and 77% (60) heterozygotes for the ΔF508 mutation; 47% (37) were male. The presence of homozygosis or heterozygosis for the ΔF508 mutation did not exhibit any statistically significant correlation with any of the parameters studied, as Table 4 shows.

Discussion

The clinical and laboratory characteristics of the 104 patients studied are close to values found in other, domestic and international, research.

Distribution by sex, race[4-6] and incidence of pulmonary manifestations[4,7,8] was comparable with what is found in the literature.

Digestive clinical manifestations were confirmed in 59.6% of the patients and the fecal fat balance was abnormal in 67.9% of these, indicating an incidence of pancreatic insufficiency below published figures.[4,7,8] The lower pancreatic insufficiency, compared with that found in the United States and Europe, may be the result of the lower prevalence of the ΔF508 mutation in Brazil, which is associated with this insufficiency.[9-14]

In the current study and in another study performed in Brazil,[5] the incidence of *meconium ileus* was 5.8 and 1.9%, respectively, which is much lower than values quoted in literature which vary from 15 to 20%.[15,16] One hypothesis

Table 2 - Statistical correlation between the patients' clinical and laboratory characteristics and the Shwachman score (n = 83)

Variables	p	Statistical test
Colonization by *Pseudomonas aeruginosa*	< 0.001	Fisher's exact test
Colonization by *P. aeruginosa* mucosa	< 0.001	Chi-square test
Forced vital capacity	< 0.001	Fisher's exact test
First second forced expiratory volume	< 0.001	Fisher's exact test
Oxygen saturation	< 0.001	Fisher's exact test
Number of infectious exacerbations during the previous years' follow-up	0.045	Chi-square test
Indications for Dornase Alpha use	0.019	Chi-square test
Indications for a regular respiratory physiotherapy program	0.017	Chi-square test
Indications for home oxygen therapy	< 0.001	Chi-square test
Sex	0.810	Chi-square test
Sweat chloride levels	0.656	Chi-square test
Colonization by *Sthaphylococcus aureus*	0.058	Fisher's exact test
Colonization by *Burkholderia cepacia*	0.431	Chi-square test
Presence of the ΔF508 mutation	0.230	Fisher's exact test
Presence of one or two ΔF508 mutations	0.669	Fisher's exact test
Current age	0.487	Chi-square test

Table 3 - Statistical correlation between the patients' clinical and laboratory characteristics and the presence or absence of the ΔF508 (n = 96)

Variable	p	Statistical test
Fecal fat levels	0.005	Chi-square test
Sex	0.058	Chi-square test
Race	1	Fisher's exact test
Incidence of pulmonary manifestations	0.681	Fisher's exact test
Digestive clinical manifestations	0.079	Chi-square test
Incidence of *meconium ileus*	0.579	Fisher's exact test
Age at onset of symptoms	0.673	Mann-Whitney
Current weight	0.368	Fisher's exact test
Diabetes mellitus	0.570	Fisher's exact test
Colonization by *Sthaphylococcus aureus*	0.751	Fisher's exact test
Colonization by *Pseudomonas aeruginosa*	0.067	Fisher's exact test
Colonization by *P. aeruginosa mucosa*	0.525	Chi-square test
Colonization by *Burkholderia cepacia*	1	Fisher's exact test
Forced vital capacity	0.089	Fisher's exact test
First second forced expiratory volume	0.723	Fisher's exact test
Presence of bronchiectasis	1	Fisher's exact test
Presence of hepatomegaly	0.327	Fisher's exact test
Shwachman score	0.230	Fisher's exact test
Number of infectious exacerbations during the previous years' follow-up	0.298	Fisher's exact test
Indication of pancreatic enzymes	0.265	Chi-square test
Indication of respiratory physiotherapy	0.351	Fisher's exact test
Indications for Dornase Alpha use	0.540	Chi-square test
Indications for home oxygen therapy	0.255	Fisher's exact test
Death	1	Fisher's exact test
Age at death	0.606	Mann-Whitney
Survival curve	0.595	Wilcoxon's test

Table 4 - Statistical correlation between the patients' clinical and laboratory characteristics and the presence of the ΔF508 mutation in the homozygote and heterozygote forms (n = 78)

Variable	p	Statistical test
Sex	0.803	Chi-square test
Race	0.617	Fisher's exact test
Incidence of pulmonary manifestations	0.423	Fisher's exact test
Digestive clinical manifestations	0.966	Chi-square test
Incidence of meconium ileus	0.325	Fisher's exact test
Age at onset of symptoms	0.284	Mann-Whitney
Current weight	0.570	Fisher's exact test
Diabetes mellitus	1	Fisher's exact test
Colonization by *Sthaphylococcos aureus*	0.493	Fisher's exact test
Colonization by *Pseudomonas aeruginosa*	0.746	Fisher's exact test
Colonization by *P. aeruginosa mucosa*	0.413	Chi-square
Colonization by *Burkholderia cepacia*	0.258	Fisher's exact test
Feces fat levels	1	Fisher's exact test
Forced vital capacity	0.145	Fisher's exact test
First second forced expiratory volume	0.161	Fisher's exact test
Presence of bronchiectasis	0.646	Fisher's exact test
Presence of hepatomegaly	0.734	Fisher's exact test
Shwachman score	0.669	Fisher's exact test
Number of infectious exacerbations during the previous years' follow-up	0.835	Fisher's exact test
Indication of pancreatic enzymes	0.529	Fisher's exact test
Indication of respiratory physiotherapy	1	Fisher's exact test
Indications for Dornase Alpha use	0.051	Chi-square test
Indications for home oxygen therapy	1	Fisher's exact test
Death	0.227	Fisher's exact test
Age at death	0.352	Mann-Whitney
Survival curve	0.175	Wilcoxon's test

for why the incidence of *meconium ileus* is lower in Brazil could be that patients with cystic fibrosis die during their first year of life, before being diagnosed.

The incidence of *Diabetes mellitus* was comparable with what has been found in other published work.[4,17,18]

Age at onset of symptoms, 72.7% of the patients had had some type of clinical manifestation before 6 months of age, with a median of 3 months. This demonstrates that onset is early and serves to alert us to the possibility of a CF diagnosis. Three patients' symptoms had onset after 10 years of age and one of these, after 20 years of age. This fact is evidence of the importance of diagnosis for patients whose respiratory symptoms have onset later on.[19]

The median of age at diagnosis was 2 years and 4 months and diagnosis was made after 10 years of age in 10% of cases. Data from the *Registro Latino-americano de Fibrosis Quística*,[6] including records from Brazil, show that the mean age at diagnosis was 4.2 years. In contrast, data from the Cystic Fibrosis Foundation in 2002,[4] reveal that the median age at diagnosis in the United States is 6 months, showing that Latin America as a whole needs to increase efforts to make early CF diagnoses, as the World Health Organization emphasizes.[1]

In this sample, the difference between the median age at diagnosis and the median age at onset of symptoms was 2 years and 1 month. Mitchell et al.[20] found an average delay between symptom onset and diagnosis of 3 years. In Brazil, studies by Maróstica[21] and Espinoza[22] show that these delays were 7 months for pediatric patients and 10.7 years in those over 15 years, respectively.

While CF does not have a cure, it does exhibit significant improvement with the treatment of symptoms.[23] Recent research has shown that early diagnosis reduces morbidity[24] and highlights the importance of starting treatment for pancreatic insufficiency and malnutrition early and also respiratory physiotherapy to maintain airways unobstructed.[25] One study demonstrated that infection by *P. aeruginosa* was the main risk factor for morbidity and mortality, pointing out that early diagnosis would aid intervention at the onset of colonization by this agent and contribute to better prognosis.[26] Another study also emphasizes the importance of treating *P. aeruginosa* aggressively when it is identified for the first time.[27]

The majority of states in Brazil do not currently run neonatal CF screening and its employment generates controversy. The cost of implementing screening, in a region with a disease incidence of 1:5,000, would be R$ 25,000.00 per new case. The negative points against screening include the elevated cost, the false positive and false negative results and the fact that recent review articles have not demonstrated differences in CF progress between patients who were diagnosed by neonatal screening and those whose diagnosis was made after symptom onset.[28,29] It is suggested that greater information about CF for pediatricians, allied with easier access to diagnosis by electrolytes in sweat would be a more plausible alternative. The cost-based argument can be questioned since one recent study demonstrated that the cost of diagnosis by neonatal screening is lower than the cost of diagnosis when this is not employed.[30] Another study, in France, demonstrated that patients whose diagnosis was made by neonatal screening had better progress than those whose diagnosis was made after symptom onset.[31] It is known that delays identifying and treating *Pseudomonas* makes it eradication difficult.[27] Serum testing can detect colonization by *Pseudomonas* 6 to 12 months before cultures are positive.[32] In this light, diagnosis by neonatal screening would lead to the performance of routine serum testing making earlier detection and a more efficient attempt to eradicate this bacteria possible. There is also the hope that a vaccine against *Pseudomonas aeruginosa* will become available for patients with cystic fibrosis. Then neonatal screening would become less controversial since without it the chance to vaccinate some patients before colonization would be lost. Finally, we should remember that neonatal screening makes it possible to give the parents genetic counseling before another pregnancy occurs.

When neonatal screening is not employed, early diagnosis can indicate greater severity. One Brazilian study found that a combination of low Shwachman score, low birth weight and low age at diagnosis are indicative of worse prognosis.[33]

During the ten-year follow-up period, 17.3% of the patients died. The median age at death was 7.8 years and median post-diagnosis survival, on the study end-date, was 18.4 years. In the United States, median survival increased from 1 year, in 1940, to 20 years in 1980.[34] In 1990, CF survival in Canada and the United States was 30.9 and 27.6 years, respectively.[35] Another study quotes the life expectancy of CF patients as having increased from 8 years in 1970 to 29.5 years in 1998[36] and, according to data from the *Cystic Fibrosis Foundation*, current life expectancy in the United States is 31.6 years.[4] Mortality in the United States between 1985 and 1999 for patients between 2 and 15 years old reduced by between 45 and 70%.[37] Another study presents even more optimistic data and considers that, currently, for a newborn with CF, life expectancy is more than 40 years.[38]

In another Brazilian study, median survival, after birth, of a cohort of 111 patients diagnosed between 1970 and 1994, was 12.6 years.[39]

The low survival in our country, when compared with that of developed countries is very worrying and reflects levels from twenty years ago in such countries. We believe that certain factors may be contributing to this fact. Initially, the delay in making diagnoses may mean that patients start treatment in a phase where there has already been lung deterioration and the chance to treat *P. aeruginosa* exacerbations early may already have been missed. Furthermore, at the time of diagnosis, 70 and 56.6% respectively of our patients presented weight and stature below the tenth percentile, which values are higher than those reported in the literature, around 42 to 44%.[4,40] Malnutrition caused by delayed treatment may also contribute to a more rapid deterioration, since a relationship between malnutrition and worsening pulmonary function has been demonstrated.[41] Another

factor which could be contributing is the small number of centers specialized in treating CF. As each center covers an area and a population that are extremely large, the difficulty patients find in accessing these centers may be contributing to compromised treatment and follow-up. According to the Cystic Fibrosis Foundation guidelines, each patient should be making four visits a year, which is not possible for many of our patients. Either increasing the number of CF treatment centers or improving the transport system for these patients could contribute to more frequent follow-up appointments and reduced morbidity and mortality.

Recent studies have demonstrated worse progress among patients with cystic fibrosis whose socio-economic status is lower. Schechter et al. found that the risk of death was 3.65 times greater among the poorest patients with cystic fibrosis, who also exhibited the most deterioration in terms of values for pulmonary function and nutritional status.[42] These findings were confirmed with a very large sample of patients from the Cystic Fibrosis Foundation.[4] A recent study demonstrated that patients with a higher socio-economic status present a 40% lower risk of mortality when compare with patients of low socio-economic status.[43] This being so, the greater morbidity and mortality of our patients may have a relationship with low socio-economic status.

Sweat chloride concentration was lower than 60 mEq/l in 11 patients (10.6%). This percentage is higher than cited in the literature where some authors relate just 2% of cystic fibrosis patients presenting sweat chloride lower than 60 mEq/l.[44,45] Of these 11 patients, six (three males) had three or more sweat chloride test results lower than 60 mEq/l and diagnosis confirmed by the identification of one or two mutations. All were Caucasoids, with normal fecal fat balance and presented respiratory symptoms, but not digestive symptoms. They had all been chronically colonized by *Sthaphylococcos aureus* and *Pseudomonas aeruginosa*, five by Mucoid *Pseudomonas aeruginosa* and two by *Burkholderia cepacia*. Genetic testing found that four patients were homozygous for ΔF508 and two for ΔF508/N1303K.

The other five patients whose sweat chloride concentration was below 60 mEq/l in our sample presented both respiratory and digestive symptoms compatible with CF, improved with the use of pancreatic enzymes and were colonized by *Pseudomonas aeruginosa*, with one having the ΔF508 mutation; this being so we considered CF and they received the conventional treatment.

Cystic Fibrosis diagnoses in the face of normal sweat chloride and sodium levels have also been confirmed by other authors.[46,47] In such cases attempts should be made to confirm diagnosis with the identification of two CF mutations or by measurement of nasal potential difference.[48-50] This test is not yet performed at our service. When diagnosis cannot be established based on the suggested methods, it should be based on clinical judgement,[48] as was the case of the five patients described.

Sixty-six percent of the patients were colonized by *Pseudomonas aeruginosa*, close to what is found in literature.[4,51]

Colonization by Mucoid *Pseudomonas aeruginosa* and *Staphylococcus aureus*, respectively, had incidences of 53 and 80%, which is similar to values found in other studies.[4,7,22,52]

The presence of *Burkholderia cepacia* in five patients (5.2%) is a worrying fact since colonization by this bacteria leads to very bad prognosis and reduces survival,[53] with one study demonstrating that this reduction is by as much as ten years in comparison with patients infected by just *Pseudomonas aeruginosa*.[54] Values for *Burkholderia cepacia* prevalence, in general, vary from 5 to 15%,[4,21,55] being higher in some regions, such as Ontario in Canada, where they reach 22%.[56]

Earlier Brazilian data[21] describe 10.7% patients presenting restrictive respiratory disorder, 25% obstructive respiratory disorder and 17.9% mixed respiratory disorder, which values are also very similar to those found in our sample.

We performed genotyping for 92.31% of our patients, which represents a good percentage when compared with the Cystic Fibrosis Foundation, who genotyped 81.4% of their patients.[4] In our sample, the ΔF508 mutation was present in 50% of the 192 chromosomes studied. The other mutations were found in the following percentages: G542X (4.17%), N1303K (2.08%), G551D (1.04%), R553X (0.52%), W1282X (0.52%).

Also in Brazil, Raskin et al.[57] describe the most frequent mutations in the Brazilian population as being: ΔF508 (47%), G542X (5.5%), N1303K (2.6%), R553X (0.8%) and G551D (0.2%). These authors further state that 26% of CF patients are homozygous for the ΔF508 mutation.

The most frequently encountered mutations in the United States were:[58] ΔF508 (66.0%), G542X (2.4%), G551D (1.6%), N1303K (1.3%), W1282X (1.2%) and R533X (0.7%). In France,[59] the ΔF508 mutation was present in 67.9% of the chromosomes of a population of 2,666 CF patients, with the other most frequent mutations being: G542X (2.5%), N1303K (2%), 1717-1G → A(1.2%), R553X (0.8%) and G551D (0.7%). In Argentina, the ΔF508 mutation is present in 66% of the chromosomes of FC patients,[60] and, in Mexico, 7.2% of CF patients' chromosomes exhibit the G542X mutation.[61]

The lower incidence of the ΔF508 mutation in our country compared with data from the United States, France and Argentina, probably occurs as a result of the large amount of racial intermixing in Brazil.

Around 60% of the patients presented a Shwachman Score (SS) that was excellent or good and just 15.7% had a moderate or severe score. Henry et al.[62] analyzing 60 patients report their average SS as 78.87.

In this analysis, the SS exhibited a statistically significant correlation with colonization by *Pseudomonas aeruginosa*, colonization by Mucoid *Pseudomonas aeruginosa*, forced vital capacity, first second forced expiratory volume, transcutaneous hemoglobin saturation by oxygen, number of infectious exacerbations during the previous years' follow-up, indications for Dornase Alpha

use, indications for a regular respiratory physiotherapy program and indications for home oxygen therapy. As these parameters are individually related with the severity of clinical status, it is considered that the SS is a good general severity evaluation method. Another Brazilian study found evidence that the SS offered positive correlation with first second forced expiratory volume.[63]

In this sample, the presence of the ΔF508 mutation was associated with abnormal fat balance and pancreatic insufficiency. These data are in agreement with international literature in which a number of different authors demonstrate that the ΔF508 mutation is associated with the presence of pancreatic insufficiency.[9-13]

In this sample, homozygous ΔF508 patients did not present any differentiating characteristic when compared with heterozygotes for the mutation. There is little extant work in the literature comparing these two subsets. Farrell & Koscik[64] report that sweat chloride levels are equal for the two groups.

In Conclusion, the clinical and laboratory characteristics of the 104 CF patients studied were similar to those described for the CF populations of other countries, with the exception of: pancreatic insufficiency (less frequent), previous history of *meconium ileus* (less frequent), median for age at diagnosis (higher), median of age at death and post-diagnosis survival (lower in comparison with data from the United States and Canada), malnutrition at time of diagnosis (higher than that reported in other countries), percentage of patients with normal sweat chloride concentrations (greater than that described in international literature), incidence of the ΔF508 mutation (lower in comparison with data from the United States and Europe).

Our results also permit the conclusion that in patients who present clinical status suggestive of CF, sweat chloride concentration < 60 mEq/l does not exclude this diagnosis and genetic studies should be performed in order to attempt to define the diagnosis.

Our data allows for the conclusion that efforts towards early diagnosis and greater treatment opportunities need to be made for cystic fibrosis patients.

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