Diagnostic screening of liver disease in cystic fibrosis

Eleonora D.T. Fagundes,1 Mariza L.V. Roquete,2 Francisco J. Penna,3 Francisco J.C. Reis,4 Cristiano G. Duque4

Abstract

Objective: cutaneous reaction after BCG revaccination has been cause of concerns due its magnitude. Would it be intense enough to discourage its use in school-age children? The objective of this study is to describe the evolution of BCG vaccination site between 48 hours and 10 weeks post-revaccination.

Methods: descriptive study, resultant of a prospective, and partially retrospective assessment of 106 patients with CF. Liver disease was defined by the presence of firm hepatomegaly (>2.5 cm from the right costal margin), and/or splenomegaly, and/or persistent and significant increase (>1.5 times the upper limit of normality, over six months) of at least two serum liver enzymes (alanine aminotransferase - ALT, aspartate aminotransferase - AST, alkaline phosphatase - ALP, -glutamyl transpeptidase - GGT).

Results: hepatomegaly was verified in seven patients (6.6%) and splenomegaly in five (4.7%). AST activity was altered in 18.9% of the patients, ALT in 9.4%, GGT in 11.3%, and ALP in 46.2%. Significant and persistent increase in liver enzyme activities was verified in nine patients (8.5%). Ten patients with CF (9.4%) fulfill the criteria for liver disease. Other causes of liver disease were excluded. The mean age of the patients with liver disease was 7.7 years. There was absolute predominance of the male sex. All the patients are without symptoms.

Conclusions: The prevalence of liver disease associated with CF was 9.4%. The frequent and transitory insignificant elevations of liver enzymes are well documented in the literature. Its significance as a predictor of liver disease has not been determined yet. However, the results of this study enhance the need for longitudinal assessment in order to define cases of liver disease in CF.


Introduction

Cystic Fibrosis (CF) is the most common lethal genetic disease among the white population, and the most frequent cause of chronic progressive pulmonary disease and pancreatic insufficiency in childhood. Liver cirrhosis was recognized as a complication of cystic fibrosis by Andersen1 in 1938, but, until recently, the importance of liver disease was overshadowed by the exuberance of lung and pancreatic...
The earlier diagnosis, the aggressive management of lung disease and a more satisfactory approach to nutritional needs have led to the progressive improvement in the survival of patients. With this, the prevalence of liver disease among patients with cystic fibrosis increased, and this subject has gained importance among families and professionals who care for CF children.

The onset of liver disease occurs at an early age, but it is generally asymptomatic during childhood. Complications, such as cirrhosis and portal hypertension, occur with a greater frequency in adolescents and young adults. Although the principal cause of death in patients with cystic fibrosis continues to be respiratory insufficiency, the complications caused by liver disease contribute to the rise of morbidity. On the other hand, ursodeoxycholic acid (UDCA) therapy, which seems to delay the progression of liver disease, required that the disease be better understood so that early diagnosis could be established and the prognosis of these patients could be improved.

The early diagnosis of liver disorders is still difficult. Universally accepted criteria have not been established yet, which explains the existence of different prevalence reports. The criteria for the diagnosis of liver disease in CF differ greatly among several authors. Some use only clinical criteria, while others use laboratory alterations, imaging exams and histopathological findings. Nevertheless, there are limitations to all these criteria, especially when they are used separately. Even liver biopsy has its limitations in relation to sensitivity, due to the focal nature of initial lesions. In addition, this procedure is so invasive for this kind of patient that clinical examination remains the “gold standard” in relation to the other diagnostic criteria.

The objective of this study is to determine the prevalence of clinical and biochemical alterations suggestive of liver disease in patients with cystic fibrosis attended at the Cystic Fibrosis Clinic at Hospital das Clínicas of Universidade Federal de Minas Gerais (UFMG), to describe the patients with liver disease and compare them with patients who are free of disease, in relation to the diversity of clinical and laboratory variables.

Methods

One hundred six patients with confirmed CF diagnosis up to December 1998 were included in the study.

The diagnosis of liver disease was defined through clinical and/or biochemical criteria. The clinical exam was considered abnormal when splenomegaly (presence of palpable spleen) and/or hepatomegaly were detected, defined as the presence of a palpable liver at more than 2.5 cm from the RCM (right costal margin), of firm consistency. Abnormal biochemical results consisted of persistent and significant rise, of at least 1.5 times the upper limit of the reference interval (ULRI), of at least two enzymes (AST - aspartate aminotransferase, ALT - alanine aminotransferase, AP - alkaline phosphatase, GGT - gamma-glutamyl transpeptidase), for a period of more than six months.

The physical examination focused on the digestive tract and was performed by a single researcher. The distance from the liver border to the RCM and to the xiphoid appendix, and the size of the spleen in relation to the left costal margin (LCM) were measured. Liver consistency (normal, firm, hard) and liver border (smooth or rhomboid) were described.

According to the recommendation of the American Cystic Fibrosis Foundation, liver biochemistry should be performed annually. Based on ULRI, the results of liver enzyme activity were grouped as follows: norma (less than or equal to 1 time the ULRI), 1.0 to 1.5 times the ULRI and greater than or equal to 1.5 times the ULRI. During the study, biochemical exams were repeated after six months in patients who presented abnormal results in the first dosage. Abnormal results obtained prior to this study were also considered, particularly in the case of patients who had already used UDCA. In patients with clinical alterations and laboratory exams suggestive of liver involvement, other causes of liver disease were ruled out, such as Wilson’s disease, hepatitis B and C, alpha-1 antitripsin deficiency and autoimmune hepatitis. In patients who presented isolated splenomegaly, without hepatomegaly, other diagnostic hypotheses, such as hematological and infectious diseases were discarded.

The study consisted of a descriptive analytical study, based on the prospective and partially retrospective evaluation of the patients. The 106 patients diagnosed, up to December 1998, were evaluated and followed up from March 1999 to June 2000.

The database was developed and analyzed by the public domain program EPI-Info, version 6.

The group of patients with liver disease was compared with the group of individuals without the disease with regard to age, general clinical status evaluated by the Shwachman score, colonization pattern of the lung by Pseudomonas aeruginosa and Burkholderia cepacea, FVC (forced vital capacity) and FEV1 (forced expiratory volume in one second) indexes, length of hospital stay (days) due to exacerbation of lung status, daily requirement of lipase/kg to control steatorrhea, and weight/age and height/age Z score. Student’s t test was used for comparing the means, and Kruskal-Wallis test for the medians. The chi-squared ($\chi^2$) test, with Yates’ correlation, and Fisher’s exact two-tailed test, if necessary, was used for comparing ratios. Statistical significance was established at less than 0.05 ($p<0.05$).

The study was approved by the Ethics and Research Committee of UFMG. Consent for participation in the study was obtained from parents, guardians, and/or the patient.
Results

Of the 106 patients studied, 54 were male (50.9%). The age of the patients varied from seven months to 24 years, with an average of 10.2 ± 6.3 years and a median of 9.6 years.

The findings of the physical exam are shown in Table 1. The liver was palpable in 45 patients, in seven of them a firm liver was palpable beyond 2.5 cm from the RCM. The spleen was palpable in five patients, three of whom presented only isolated splenomegaly, without the presence of a palpable liver. The physical exam yielded abnormal results in 9.4% of the patients.

Alterations to at least four liver enzymes were found in 54.7% of the patients. The laboratory evaluation, according to each studied enzyme, is shown in Table 2.

Significant and persistent biochemical alterations were observed in nine patients (8.5%). One patient, age 8.5, presented persistently normal aminotransferases, AP and GGT, although he had had splenomegaly from the age of 4.5 years. Despite normal results, the patient was considered to have liver disease, in view of physical examination and the exclusion of other causes of liver disease and splenomegaly.

Therefore, among 106 patients, 10 patients with cystic fibrosis (9.4%) presented clinical and/or biochemical alterations compatible with CF-associated liver disease.

The average age of the patients with alterations suggestive of liver disease was 7.7 ± 0.4 years, range from 1.3 to 17.4 years, with a median of 5.7 years. There was an absolute predominance of males. Only one patient had a history of neonatal cholestasis associated with severe anemia and hypoalbuminemia. None of the 10 patients presented a history of meconium ileus. The clinical characteristics of the 10 patients with liver disease are shown in Table 3.

The average age at which the first clinical or biochemical alterations suggestive of liver disease were reported varied from 0.2 to 12.0 years, with an average of 4.8 ± 4.5 years and a median of 3.1 years. In four patients, physical exam alterations preceded biochemical alterations and, in another four, laboratory exam alterations were the first manifestations suggestive of liver disease. In two patients, clinical and biochemical alterations were detected at the same time.

The variation of liver enzyme activity was evident during the first years of monitoring, alternating normal and abnormal results. As age increased, these variations became less frequent.

### Table 1 - Findings of the physical examination of 106 patients with cystic fibrosis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Absolute frequency</th>
<th>Relative frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable liver</td>
<td>45</td>
<td>42.5</td>
</tr>
<tr>
<td>Liver &gt; 2.5 cm from RCM, firm consistency</td>
<td>7</td>
<td>6.6</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>Isolated splenomegaly</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>Altered physical exam*</td>
<td>10</td>
<td>9.4</td>
</tr>
</tbody>
</table>

RCM: right costal margin.
* presence of palpable spleen and/or hepatomegaly, defined as the presence of palpable liver, with firm consistency, > 2.5 cm from the RCM.

### Table 2 - Laboratory alterations in 106 patients with cystic fibrosis

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>&gt;1.0 and &lt;1.5 times the ULRI* (%)</th>
<th>&gt;1.5 times the ULRI (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>2.8</td>
<td>6.6</td>
<td>9.4</td>
</tr>
<tr>
<td>AST</td>
<td>10.4</td>
<td>8.5</td>
<td>18.9</td>
</tr>
<tr>
<td>AP</td>
<td>17.0</td>
<td>29.2</td>
<td>46.2</td>
</tr>
<tr>
<td>GGT</td>
<td>1.9</td>
<td>9.4</td>
<td>11.3</td>
</tr>
</tbody>
</table>

* upper limit of reference interval.
All the patients with liver disease presented some alteration on the ultrasound exam. The most frequent alteration was to the parenchyma (50%), followed by periportal fibrosis and nodularity of the liver border. Steatosis was visible in two patients and atrophic gallbladder, in only one. Portal-systemic collaterals were detected in two patients. Three patients had already used UDCA before this study, with doses varying from 300 to 400 mg a day, or 8 to 10 mg/kg/day. The doses used were significantly lower than recommended, due to the cost of medication, thus interfering with the treatment scheme. The indication of UDCA to the three patients was determined by persistently abnormal biochemistry. Two patients maintained oscillating biochemical alterations after using UDCA. One patient obtained good results, with normalization of aminotransferases and of GGT after approximately two years of UDCA therapy. However, alkaline phosphatase activity, continued to be abnormal, with oscillations. All the patients remained asymptomatic. One patient, age 17.4, with severe splenomegaly, has shown hypersplenism, presenting reduced platelet count (64,000 platelets/mm³) and leukopenia (total leukocyte count of 2,800/mm³). The upper digestive endoscopy, done in 1994, had already shown small esophageal varices. Nevertheless, the patient has not had, to this point, any digestive hemorrhage episodes.

The groups of individuals with and without liver disease were compared according to several variables. In relation to age, general clinical status evaluated by Shwachman score and pattern of lung colonization by *Pseudomonas aeruginosa* and *Burkholderia cepacia*, the two groups are comparable. In relation to FVC and FEV1, even though they tended to be lower among patients with liver disease, this difference was not statistically significant (p=0.072 and 0.094, respectively). The median length of hospital stay (days) due to exacerbation of lung status was also compared (Table 4), and showed to be significantly greater in the group with liver disease (p=0.0186).

The medians for lipase units/kg/day necessary to control steatorrhea were compared between the two groups (Table 5). The median in the group with liver disease was higher than that of the group without liver disease, and this difference was statistically significant (p=0.023).

Even though the weight/age and height/age Z scores tended to be lower in the group with liver disease, this difference was not statistically significant (p=0.16 for both scores).

### Discussion

Any clinical or epidemiological study is subject to bias at different stages, from data collection to the final analysis of the data. In studies about liver disease in CF, analysis bias is perhaps the major one, as there are neither sensitive markers of hepatic involvement nor standardized diagnostic criteria. In this study, clinical and laboratory criteria were adopted for the definition of liver disease since they are...

<table>
<thead>
<tr>
<th>Sex</th>
<th>Race</th>
<th>Age*</th>
<th>Mutation</th>
<th>PI</th>
<th>Age* first alterations</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>M</td>
<td>2.4</td>
<td>ND</td>
<td>yes</td>
<td>1.7</td>
<td>no</td>
</tr>
<tr>
<td>2.</td>
<td>M</td>
<td>1.5</td>
<td>ND</td>
<td>yes</td>
<td>0.2</td>
<td>no</td>
</tr>
<tr>
<td>3.</td>
<td>M</td>
<td>17.4</td>
<td>N5/N5</td>
<td>yes</td>
<td>12.0</td>
<td>hypersplenism, esophageal varices, asymptomatic portal hypertension</td>
</tr>
<tr>
<td>4.</td>
<td>F</td>
<td>16.5</td>
<td>DF508/G542X</td>
<td>yes</td>
<td>10.3</td>
<td>asymptomatic portal hypertension</td>
</tr>
<tr>
<td>5.</td>
<td>M</td>
<td>11.6</td>
<td>G542X/N5</td>
<td>yes</td>
<td>6.9</td>
<td>asymptomatic portal hypertension</td>
</tr>
<tr>
<td>6.</td>
<td>M</td>
<td>1.3</td>
<td>ND</td>
<td>yes</td>
<td>0.7</td>
<td>no</td>
</tr>
<tr>
<td>7.</td>
<td>M</td>
<td>1.7</td>
<td>ND</td>
<td>yes</td>
<td>1.8</td>
<td>no</td>
</tr>
<tr>
<td>8.</td>
<td>M</td>
<td>12.8</td>
<td>DF508/DF508</td>
<td>yes</td>
<td>9.2</td>
<td>portal hypertension, death due to RI</td>
</tr>
<tr>
<td>9.</td>
<td>M</td>
<td>2.8</td>
<td>DF508/DF508</td>
<td>yes</td>
<td>1.6</td>
<td>no</td>
</tr>
<tr>
<td>10.</td>
<td>M</td>
<td>8.5</td>
<td>N5/N5</td>
<td>no</td>
<td>4.5</td>
<td>no</td>
</tr>
</tbody>
</table>

PI: pancreatic insufficiency; RI: respiratory insufficiency; M: male; F: female; W: white; NW: non-white; N5: none of the five most frequent mutations (DF508, G542X, N1303K, R553X, G551D); ND: non-defined; *in years
easily available to the majority of Brazilian reference centers that treat patients with cystic fibrosis. In spite of their limitations, these criteria are still the "gold standard" for the diagnosis of CF-associated liver disease. Ultrasonographic alterations were not used in the screening of liver disease, due to the absence of studies that could verify the specificity of the observed alterations. Histopathology was also not incorporated due to the possibility of sampling error and because of the focal nature of the lesions, which does not justify submitting asymptomatic patients to the inherent risks of a liver biopsy, as no effective treatment for CF-associated liver disease is yet available. Wilschanski et al. did not include hepatomegaly in the diagnostic criteria due to possibility of observer bias. In spite of this risk, we opted to include physical examination, due to the importance of incorporating clinical parameters in the follow-up of the patients.

Controversy also exists over biochemical alterations. Lindblad et al. highlighted the lack of association between biochemical exams and liver disease in those younger than three years old. Ling et al. verified that, aside from biochemical alterations, hepatomegaly and ultrasonographic abnormalities also present an intermittent character, which could represent an important observer bias in cross-sectional studies. This way, longitudinal follow-up is important to define cases of liver disease, which should not be labeled as such after one single evaluation. In this study, the patients were followed, prospectively, for an average period of one and a half years. They presented variable results in the biochemical exams and discrete alterations on physical examination, but met the diagnostic criteria for CF-associated liver disease.

The evidence of hepatosplenomegaly on physical examination is extremely variable. Scott-Jupp et al. found a prevalence of isolated hepatomegaly in 1% of patients, 0.3% of isolated splenomegaly and 2.9% of hepatosplenomegaly. On the other hand, Gaskin et al. and Colombo et al. found a much higher frequency of hepatomegaly (30%). In this study, the frequency of hepatomegaly (6.6%) was almost twice as high as that reported by Scott-Jupp et al., but much lower than that reported by Gaskin et al. and Colombo et al. This difference in prevalence can be attributed, for the most part, to the different criteria used for the definition of hepatomegaly. Splenomegaly was observed in 4.7% of the patients; a similar frequency of 5.8% was verified by Colombo et al. Physical examination yielded abnormal results in 9.4% of the patients, which is consistent with the literature (1.4 to 17%).

Alterations to liver enzymes, especially their transitory elevations, are more frequently reported than clinical alterations. In this patient population, 54.7% of the patients exhibited alterations to at least one of the four liver enzymes analyzed in the cross-section. AP was the enzyme most

Table 4 - Comparison of the median length of hospital stay (days) due to exacerbation of lung status between groups with and without liver disease

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>mean</th>
<th>standard deviation</th>
<th>median</th>
<th>statistics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
<td>10</td>
<td>24.2</td>
<td>37.9</td>
<td>7.0</td>
<td>p=0.0186</td>
</tr>
<tr>
<td>No liver disease</td>
<td>96</td>
<td>5.6</td>
<td>15.4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test.

Table 5 - Comparison of the medians of lipase units/kg/day necessary to control steatorrhea between the groups with and without liver disease

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>mean</th>
<th>standard deviation</th>
<th>median</th>
<th>statistics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
<td>10</td>
<td>2.488</td>
<td>2.051</td>
<td>1.930</td>
<td>p=0.023</td>
</tr>
<tr>
<td>No liver disease</td>
<td>96</td>
<td>1.334</td>
<td>1.979</td>
<td>362</td>
<td></td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test.
frequently altered (46.2%). AST was the second most frequently altered enzyme (18.9% of the patients), followed by GGT (11.3%) and ALT (9.4%). The alteration to ALT activity, which is more specific for liver disease, has been observed at a lower frequency than AST, similarly to what occurs in alcoholic hepatitis. The reasons for this finding were not determined. In a cross-section, Patirquin et al. found an elevation of AST, ALT and GGT of respectively 26%, 15% and 16%, in a population of 189 patients with cystic fibrosis.

Ling et al. found biochemical alterations in 42% of 124 patients, 27% of whom did not present any other alteration suggestive of liver disease. Sokol et al. found a high frequency of children with biochemical alterations in the first years of life, reaching more than 50%, with a decrease up to the age of 8. The transitory elevation of liver enzymes is very common among patients with cystic fibrosis; however, the significance of this finding for the prediction of liver disease has not yet been determined.

On the other hand, persistent and significant elevation of liver enzymes should be considered indicative of liver disease. Colombo et al. found persistent alterations to liver biochemistry in 16.9% of patients. In this study, the prevalence of these alterations was lower (8.5%). This difference can be explained by the heterogeneity of the populations studied and the different cutoff points used for the definition of abnormal biochemistry.

The prevalence of CF-associated liver disease in this study, defined by clinical and/or biochemical criteria, was 9.4%. The prevalence reported by Colombo et al. was 17% among 189 patients older than three years, using clinical, biochemical and ultrasonographic criteria. Wilschanski et al. verified a prevalence of 28%, using biochemical and ultrasonographic criteria. The lower prevalence verified in this study can be explained by the use of different diagnostic criteria. In addition, the majority of authors do not characterize the study population, and this patient population is different in terms of race composition, age and survival. With respect to survival, for example, in the USA the 1989 median was 27 years and in Canada, 30 years. In Minas Gerais, the median estimate of survival in the 1970s was 5.4 years, in the 1980s it rose to 9.2 years, and in the first four years of the 1990s, the average survival was 12.6 years. This perfectly demonstrates the difference of almost 20 years in relation to the USA and Canada indexes, confirming that the Brazilian patient population cannot yet be compared to that of the USA and Canada.

The average age at diagnosis of liver disease was 8.7 years in the patient population of Psacharolopoulos et al. In the patient population of Noble-Jamieson et al., the age varied from two to 12 years. Half of the patients presented with hepatosplenomegaly and the other half with elevated enzyme activity, as occurred with this patient population. Among the patients studied by Scott-Jupp et al., the average age of presentation was 9.8 years and , the most frequently detected clinical sign was an increase in the size of the liver or spleen, or both. In the patient population analyzed by Feigelson et al., cirrhosis always manifested itself before puberty. These authors did not observe onset of cirrhosis after the age of 18. In spite of variable data, we can conclude that even though the signs suggestive of liver disease can occur early on, the complications of the disease only occur at the end of the first or at the beginning of the second decades of life. In the patient population of Wilschanski et al., the patients with symptoms of liver disease were significantly older than the asymptomatic ones.

Aminotransferases can be normal or slightly elevated in patients with clinically evident disease, as occurred with one of the patients with persistent splenomegaly since the age of 4.5 years. It is still important to underscore the variation of liver enzymes. As age increases, these variations become less frequent.

The morbidity of hepatic involvement is mainly associated with complications of portal hypertension, especially upper digestive hemorrhage. The incidence of CF-associated portal hypertension amounted to 2% in the patient population of Di Santagène & Blanc and to 1.9% in the patient population of Stern et al. Digestive hemorrhage, secondary to the bleeding of esophageal varices, occurred in 1% of 693 patients studied by Stern et al. The first episode of digestive hemorrhage occurred between 12 and 17 years. Hypersplenism was reported in 1.6% of the patients. All the patients with liver disease in this patient population remained asymptomatic, most likely because of their young age. One patient, age 17.4 years, with splenomegaly, developed hypersplenism, besides small esophageal varices, as shown in an upper digestive endoscopy in 1994. Three other patients also presented clinical and ultrasonographic symptoms of portal hypertension.

Mortality is more often related to lung disease, when related to liver disease, it is generally secondary to digestive hemorrhage and, very rarely, to liver failure. Until the end of the follow-up period, two deaths occurred among a total of 106 patients studied, both due to respiratory insufficiency. One of the patients also had liver disease with established portal hypertension.

There are studies that reveal that lung disease is less severe in those patients with liver disease. On the other hand, liver cirrhosis, with portal hypertension, can contribute to a decline in lung function due to the restriction caused by hepatosplenomegaly and ascites. However, Wilschanski et al. did not find any difference as to the severity of lung status, even among patients with liver disease who were symptomatic and who had portal hypertension. In this patient population, no difference was observed between the groups with and without liver disease in relation to colonization by P. aeruginosa and B. cepaceae. Ling et al., as well as Lindblad et al., also did not find differences in the colonization pattern of these bacteria among individuals with or without liver disease. As to lung function tests, the
Nevertheless, there have been reports of patients with cystic fibrosis who had pancreatic insufficiency. The necessity of pancreatic enzymes was significantly reduced in patients with liver disease compared to those without. In a study conducted by Colombo et al., all the patients with liver disease had pancreatic insufficiency. Nevertheless, there have been reports of patients with cystic fibrosis with preserved pancreatic function. In this study, the median length of hospital stay (days) due to exacerbation of lung status was significantly lower in the group with liver disease. Lung restriction by hepatoplenomegaly could predispose patients to these exacerbations.

Hepatobiliary disease has been frequently reported in patients with pancreatic insufficiency. In the study conducted by Colombo et al. and Wilschanski et al., all the patients with liver disease had pancreatic insufficiency. Nevertheless, there have been reports of patients with cystic fibrosis with preserved pancreatic function. In this study, the median units of lipase/kg/day necessary to control steatorrhea in the group with liver disease was higher than in those without liver disease (p=0.018). Thus, liver disease seems to be a part of a more serious CF picture, which includes difficulty in controlling pancreatic insufficiency, and a rise in the daily necessity of pancreatic enzymes. In a series of nine patients with liver cirrhosis secondary to CF, there was a significant improvement of steatorrhea after liver transplant, with a significant reduction in the daily necessity of pancreatic enzymes. Other studies have not demonstrated any difference as to nutritional status between those with and without liver disease, which is similar to what we found in this patient population. Even though the mean z score for weight/age and height/age tended to be lower among patients with liver disease, this difference was not statistically significant (p=0.16 for both).

The prevalence of CF-associated liver disease, in the Cystic Fibrosis Clinic of the HC of UFMG was 9.4%, based on clinical and/or biochemical criteria. The highest frequency of transitory and poorly significant elevations of liver enzymes emphasizes the need of sequential evaluations to define liver disease in CF. Pancreatic insufficiency and the severity of the lung status, determined by the necessity of hospitalization, were associated in a statistically significant manner to liver disease in CF. However, longitudinal studies are necessary in order to establish the real participation of these factors as predictors of liver involvement in CF.

References
