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Diagnosing hepatobiliary disease in cystic fibrosis: a challenge

Dear Editor,

We would like to congratulate our peers at the *Universidade Federal de Minas Gerais, Hospital das Clínicas*, who have ignited relevant discussion on the subject of cystic fibrosis (CF) with their experiences.[1-7]

The article published under the title "*Validation of the Williams ultrasound scoring system for the diagnosis of liver disease in cystic fibrosis*" analyzed 70 CF patients, ten of whom were defined as having liver disease on the basis of biochemical abnormalities and/or evidence of hepatosplenomegaly. Of these ten, just five exhibited an ultrasound score (USS) > 3 (four patients with scores of 4-7 and one patient with a score of 8).[1]

The score proposed by Williams et al. in 1995 was able to demonstrate a good level of correlation between ultrasound findings and qualitative and quantitative biochemical indicators of liver function.[8] Sixty-eight adults took part in that study and there was a real need for it to be validated for the pediatric population, which was the objective of the article in question. However, in order for validation tests to be performed it is necessary to find a gold standard for diagnosis. At this point we come up against the question, "what is the best method for diagnosing CF liver disease: clinical evidence of liver disease or biochemical findings?"

The North-American consensus document proposes that a hardened edge of the liver, in conjunction with splenomegaly, is a clinically significant indicator of liver involvement in these patients. It further states that, due to the pulmonary hyperextension that is very common in these patients, total liver measurement is considered the reference for a diagnosis of hepatomegaly, in place of simple palpation of the organ below the right costal margin. The presence of hepatic enzyme (AST, ALT, alkaline phosphatase, GGT) and bilirubin levels in serum above 1.5 times the normal reference value for more than 3-6 months, with other causes excluded, is an indicator for liver disease.[9]

Fagundes et al.[1] defined liver disease based on clinical and biochemical criteria. They defined the clinical examination as abnormal when the spleen was palpable and/or hepatomegaly was found, defined as the presence of a firm, palpable liver more than 2.5 cm below the right costal margin (RCM). Abnormal biochemistry was defined as the persistent and significant increase (1.5 times the normal reference value) of at least two of the enzymes (AST, ALT, alkaline phosphatase, GGT), for a period greater than 6 months.

In our experience hepatic enzymes (AST, ALT, alkaline phosphatase, GGT) were incapable of identifying four out of five patients with CF and advanced liver disease, who underwent liver transplant and whose USS was $\geq$ 8. This does not surprise us since normal hepatic enzyme values can be found in patients with compensated and uncompensated cirrhosis, and are common among patients with biliary patients.[9]

We have used the score proposed by Williams et al.[8] since 1997[10] and reviewed the examinations of 131 patients with CF diagnoses treated at the Child Pneumology Sector at the *Hospital de Clínicas* in Porto Alegre. With the objective of evaluating the sensitivity and specificity of the biochemical tests we performed an assessment in the opposite direction to that undertaken by Fagundes et al.[1] We defined liver disease as a USS of $\geq$ 6 and proceeded to test sensitivity, specificity and positive and negative predictive values. The patients that our team studied were similar in terms of mean age (9.3±4.9 years) and the prevalence of the male sex (53.4%) to those described by Fagundes et al.[1] Thirty-four (26%) patients exhibited a USS $\geq$ 6. Of these 55.9% presented some abnormal test result or other, compared with 26.8% of the subset with a USS < 6 (p = 0.003). Each laboratory test (AST, ALT, alkaline phosphatase, GGT) was compared in isolation with the USS result. We observed a low sensitivity for the laboratory tests in diagnosing of CF liver disease.[11]

What is the difference between the two experiments? Were the ultrasound examiners different? The number of patients studied? An analysis of table 4, published with the article in question, gives evidence of a very wide range in the confidence intervals referring to the ultrasound score. This can be explained by the restricted number of cases identified by the authors and merits consideration.

We think that the authors' conclusions that the ultrasound score is a method with low sensitivity for the diagnosis of CF liver disease may be hasty. We share in the "challenge" that is the diagnosis and treatment of hepatobiliary disease in these patients. We believe that, currently, early diagnosis of this condition lies in the sum of clinical, laboratory and ultrasound data.

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Authors' reply

We are grateful for the interest in the work undertaken at our service and for the chance to share in the experiences of our peers at the *Hospital das Clínicas* in Porto Alegre with cystic fibrosis (FC) liver disease.

One of the principal challenges that studies of FC liver disease face is the definition of the condition, since there are no sensitive markers of liver involvement nor uniform diagnostic criteria. Indeed, observation and experience with these patients has shown that no criterion, whether clinical, biochemical or ultrasound findings, used in isolation offers adequate sensitivity and specificity for diagnosis. In other words, clinical evidence of liver disease does not constitute better criteria for diagnosis than do biochemical findings, or vice-versa; these criteria are complementary. On the other hand longitudinal follow-up is important for the definition of cases of liver disease and these should not be labeled as such at a single evaluation due to the intermittent character, not just of the biochemistry, but also of ultrasound and physical examination findings.[1]

The North-American consensus document[2] recommends screening by means of regular clinical and biochemical examinations. While we understand their limitations, this justifies their use in this study as the gold standard. Abdominal ultrasound is the imaging method most widely employed for the diagnosis of hepatobiliary involvement in FC. However, the American consensus[2] considers ultrasound examination of little use for detecting liver disease in FC, because steatosis is similar to periportal fibrosis, both of which are very common among CF patients. Despite these limitations, ultrasound is used ever more frequently.

It is important to recognize the difficulties that exist when defining hepatomegaly in CF patients. In general, the palpable liver present in patients with chronic lung disease is attributed to a fallen diaphragm secondary to pulmonary hyperinflation. Nevertheless, experience shows that older children who present with significant hyperinflation and increased antero-posterior (AP) diameter do not generally have palpable livers. It is believed that the increase in AP diameter contributes to accommodating the liver within the thoracic chamber, reducing the dropping effect. Some authors use liver measurement in attempts to reduce errors, despite the percussion difficulties resulting from the interposition of the lungs secondary to hyperinflation. Therefore, the consensus document states that the texture of the liver edge is more important than its measurements. A palpable liver more than 2.5 below the right costal margin (RCM) should be considered abnormal at any age. Livers forced downwards by lung disease should be differentiated from an involved liver by means of its consistency and the characteristics of its edge. A liver that can be palpated below the 2.5 cm purely as a result of pulmonary drop should be soft and have a thin, smooth edge. A palpable spleen should also be considered abnormal under any circumstances.[2,3]

With respect of the results presented by our peers, the same doubt with respect of the criterion chosen as gold standard for diagnosing FC liver disease is applicable. According to the American consensus document,[2] ultrasound findings are of little use for detecting and quantifying fibrosis and cirrhosis if CF patients, from which springs its limitation as a diagnostic criterion when used in isolation and, consequently, as a gold standard for testing the sensitivity and specificity of other tests. In common with our peers, we found a correlation between the ultrasound score and clinical and/or biochemical abnormalities. According to our criteria, the liver patients exhibited higher scores than patients without liver disease, showing a positive association, in common with the data from Porto Alegre. Nevertheless, we do not consider adequate to test the sensitivity and specificity of the biochemistry employed, using just the ultrasound score as a gold standard.

While the confidence intervals for sensitivity and specificity are wide, due to the small number of liver patients identified in our study, we believe that the major difference between the two studies is in the choice of diagnostic criteria, Screening for hepatopathy by ultrasound alone, as our peers have done, will result in fatal delay or underdiagnosis. For this reason we agree with the conclusion that the diagnosis of FC liver disease must be based on the sum of, clinical, biochemical and ultrasound findings.

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Esophageal achalasia and eosinophilic esophagitis

Dear Editor,

I would like to add some data on the subject of esophageal achalasia. The article presented the diagnostic and therapeutic propaedeutic for the condition brilliantly,[1] but omitted to include data related to the results of biopsies. This is an important data in that it may show suggestive abnormalities of the associated pathologies related to the origin of the esophageal achalasia. As examples it is worth citing systemic lupus erythematosus, sarcoidosis and eosinophilic esophagitis (EE).[2]

Eosinophilic esophagitis is a cause of esophageal dysmotility that is being described with ever increasing frequency, as it becomes better known and investigated by physicians.[3] Its clinical presentation is very similar to gastroesophageal reflux, presenting with symptoms such as abdominal pains, vomiting and dysphagia, among others, which do not respond to conventional anti-reflux treatment. Additionally pH measurements reveal a tendency to high pH values.[4] Diagnosis is made by biopsy which will reveal the presence of eosinophils in the lower third of the esophagus with numbers greater than 20 or 24 per 40-times magnification field. In general it will progress to more serious motility disorders and the presentation of odynophagia, food impaction, weight loss, failure to thrive and cachexia.[2-4]

Despite being more often associated with esophageal wall thickening and stenosis, the association between esophageal achalasia and an eosinophilic esophagitis has been described.[2,5] In a series of 42 patients with diagnoses of esophageal achalasia, subjected to thoracic esophagectomy, with esophageal fragments studied microscopically, 22 patients (52%) presented eosinophila in the muscular layer.[6] The role of these eosinophils in the formation of achalasia injuries is not yet well understood.[7] In EE, in addition to procedures to permit the passage of food, such as dilatation or esophageal surgery, it is also necessary to investigate possible food allergens, which are found in 50 to 80% of affected individuals.[8] In general exclusion of the food allergen leads to considerable symptomology improvements. However, in some cases symptoms will persist or recur, making it necessary to prescribe drugs such as oral or inhaled corticoids or even antileucotrienes.[9] The absence of food allergens is also corroborated with the use of these drugs.[8,9]

The growing knowledge and increasing number of case histories of patients with EE, primarily children, but also adults,[10] was the motive for this letter, on the aspect of both achalasia and esophageal stenosis – both associated with this disease which is acquiring significant importance all over the world.

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