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● *Original Contribution*

LONGITUDINAL TRANSIENT ELASTOGRAPHY MEASUREMENTS USED IN FOLLOW-UP FOR PATIENTS WITH CYSTIC FIBROSIS

Stephanie Van Biervliet,*† Hugo Verdievel,‡ Saskia Vande Velde,† Ruth De Bruyne,† Danny De Looze,* Xavier Verhelst,‡ Anja Geerts,‡ Eddy Robberecht,* and Hans Van Vlierberghe‡

*Cystic fibrosis Centre Ghent, Ghent University Hospital, Ghent, Belgium; †Department of Pediatric Gastroenterology and Hepatology, Ghent University Hospital, Ghent, Belgium; and ‡Department of Adult Hepatology, Ghent University Hospital, Ghent, Belgium

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Abstract—Cystic fibrosis–related liver disease (CFLD) is diagnosed using a combination of criteria. Transient elastography (TE), an ultrasonographic method to evaluate liver stiffness, can differentiate patients with and without liver disease. This retrospective study (2007–2013) aimed to detect developing CFLD using consequent TE measurements. All cystic fibrosis patients with TE measurements between 2007 and 2013 (n = 150, median age 17 (9–24) y) were included, of which 118 had a median of three (range, 2–4) measurements with an interval of 1 (1–2) y. Twenty (14%) had CFLD at the first TE measurement; five (3%) developed CFLD during follow-up. The median TE value in CFLD was 14 kPa (8.7–32.2) compared with 5.3 (4.9–5.7) in cystic fibrosis patients without liver disease (CFnoLD; $p = 0.0001$). In CFnoLD, TE was correlated with age ($p = 0.031$). A TE result >6.8 kPa had a sensitivity of 91.5% and a specificity of 91.7% in predicting CFLD, according to the receiver operating characteristics analysis. It also has a positive predictive value of 88.6% and a negative predictive value of 86.9%, increasing to 91.7% and 98%, respectively, in patients at risk (<14 y) for developing CFLD. Patients with developing CFLD had progressively increasing consecutive TE measurements. (E-mail: stephanie.vanbiervliet@ugent.be) © **2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Cystic fibrosis, Liver disease, Fibroscan, Transient elastography, Portal ultrasound.**

INTRODUCTION

Cystic fibrosis is the most widespread autosomal recessive disease among Caucasians. It is caused by a mutation in the cystic fibrosis transmembrane regulator (CFTR) gene, which codes for an anion channel expressed in epithelial cells throughout the body (Gadsby et al. 2006).

Cystic fibrosis–related liver disease (CFLD) has a cumulative incidence of 27%–35% (Colombo et al. 2002; Lindblad et al. 1999). Most cases are detected in the first decade of life (Lindblad et al. 1999). Five to ten percent will develop multi-lobular cirrhosis, leading to portal hypertension and related complications (Debray et al. 1999; Gooding et al. 2005). As a result, CFLD remains the third-leading cause of cystic fibrosis (CF) mortality (Parisi et al. 2013). Synthetic failure, however, is rare and develops slowly over the years (Gooding et al. 2005).

The pathogenesis of CFLD is largely unknown. The abnormal CFTR function in the apical membrane of the biliary epithelium leads to decreased bile fluidity and alkalinity, causing inspissated bile accumulation, inflammation and fibrosis (Parisi et al. 2013). This hypothesis, however, cannot explain why only a sub-group of patients develops CFLD and why the development occurs before puberty. Although neither CFLD development nor CFLD severity have been associated to specific CFTR mutations, it is delimited to genotypes resulting in absent CFTR function (Wilschanski et al. 1999). All patients with CFLD are pancreatic insufficient, but no association is found with nutritional status, meconium ileus or pulmonary function (Wilschanski et al. 1999). Non-CFTR genetic polymorphism studies revealed an increased risk for patients carrying the α1-antitrysin Z-allele (Bartlett et al. 2009). Other studies revealed a different expression of several genes associated with hepatic fibrogenesis

Address correspondence to: Stephanie Van Biervliet, University Hospital Ghent, De pintelaan 185, 9000 Ghent, Belgium. E-mail: stephanie.vanbiervliet@ugent.be

(Pereira et al. 2012). The genetic predisposition, independent of the CFTR gene, needs further exploration.

Recent guidelines concerning diagnosis and management of CF advocate regular screening for CFLD and follow-up of patients with CFLD for portal hypertension–associated problems and signs of liver failure (Debray et al. 2011).

Diagnosis of CFLD is complicated, as a wide spectrum of hepatobiliary diseases, including iatrogenic and extra-hepatic disease, can trouble the clinical picture. The diagnosis is currently made using criteria that include biochemistry, physical examination and ultrasound observations (Debray et al. 2011). Biochemical abnormalities are often mild and have a low sensitivity and specificity (Mueller-Abt et al. 2008). Ultrasound examination has been shown to be reliable for visualizing pronounced multi-lobular cirrhosis but not for the mild focal lesions (Mueller-Abt et al. 2008). Liver biopsy is only advocated to exclude other causes of liver disease, as it may under-estimate the severity of lesions because of their focal nature (Debray et al. 2011). It is not until pathologic changes are diffuse and pronounced that the disease becomes clinically apparent.

Liver fibrosis correlates with liver stiffness, which can be evaluated by ultrasound using different methods (de Lédinghen et al. 2007; Fraquelli et al. 2007; Soresi et al. 2014). Transient elastography (TE) is a non-invasive ultrasound technique. The progression of a mechanical wave induced by the probe is followed using ultrasound. This measurement gives a quantitative idea of liver stiffness expressed in kPa (de Lédinghen et al. 2007). Another method is acoustic radiation force impulse. This method measures the shear wave velocity induced by acoustic radiation. It has the advantage of providing tissue imaging, tissue quantification, the opportunity to avoid blood vessels or the gallbladder and the ability to examine a specific region of the liver. The measured speed (m/s) increases with increasing liver stiffness (Soresi et al. 2014). Both acoustic radiation force impulse and TE have been reported to have a similar performance for the diagnosis of severe fibrosis (Bota et al. 2013). In cystic fibrosis, the literature on patient follow-up using these techniques is limited.

This retrospective study evaluates whether consecutive TE measurements can discern patients developing liver disease from those without liver disease.

PATIENTS AND METHODS

Patients

The study is a retrospective study including all CF patients (n = 150) followed at the Ghent CF center who received at least one TE measurement between 2007 and 2013. The diagnosis of CF was made from two positive sweat chloride tests. Patients above the age of 4 y received at least one TE measurement during their annual check-up (to be able to perform reliable measurements with a medium probe, patients need to be older than 4 y). Other tests performed were a physical examination as well as a blood sample for liver enzymes. The abdominal ultrasound was scored according to Williams et al. (1995), which is the sum of a 1–3-point scoring system for coarseness of the parenchyma, nodularity of the liver edge and increased peri-portal echogenicity. A normal ultrasound score is 3, whereas severe cirrhosis receives a score of 9.

Other data collected from the patient file were age and pancreatic function. Pancreatic insufficiency was diagnosed based on fecal elastase below 200 μg/g.

Diagnosis of CFLD

CFLD is diagnosed when two of the following variables are present: hepato- and/or splenomegaly on physical examination, persistently increased transaminases or gamma-glutamyltransferase (>12 m, three consecutive blood samples, >1.5 times upper limit) and abnormal liver ultrasound or signs of portal hypertension on duplex ultrasonography (Debray et al. 2011). When patients did not fulfill at least two of these criteria, they were classified as not having liver disease (CFnoLD).

Transient elastography measurement

Liver stiffness was assessed using TE (Fibroscan, Echosens, Paris, France). The obtained result was the median of 10 validated measurements expressed in kilopascal (kPa) using an adult medium probe (for technical details see Nobili et al. 2008). The same trained technician performed all measurements. Only measurements with an inter-quartile range below one third of the median, at least 60% success rate and with an A-shaped wave were accepted (de Lédinghen et al. 2007; Fraquelli et al. 2007).

Study design

All patients with a TE measurement between 2007 and 2013 were included. Data on the TE measurement, ultrasound, liver enzymes, age and pancreatic function were retrieved from the file. Patients were followed at the Ghent University hospital CF center and received yearly check-up investigations.

Patients were classified as developing CFLD when they had no CFLD at the start of the study period but had CFLD at the end.

Because CFLD develops in the first decade, results of patients younger than 14 y were evaluated separately.

Statistical analyses and ethics

Statistics were performed with SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA). For differences