



Elastographic assessment of liver fibrosis in children: A prospective single center experience

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ABSTRACT

Background: The assessment of liver damage in various disease states relies on a combination of clinical findings, biochemical parameters and invasive tests such as liver biopsy. The ultrasound elastography has emerged as a potential alternative test, providing quantifiable information on the elasticity/stiffness of the examined-tissues. We assessed the performance of ultrasound elastography using real-time Acoustic Radiation Force Imaging (ARFI) technology in evaluating the degree of liver fibrosis in children with and without liver disease.

Methods: Children aged 0–18 years, hospitalized in the Emergency Clinical County Hospital Tg. Mures, Romania, between September 15, 2010 and January 15, 2011, were eligible for the study. Four groups were recruited as follow: patients with liver disease in the setting of various malignant disorders, children with non-malignant liver disease, overweight and obese children and healthy controls. The liver tissue elasticity was assessed in each individual using Shear Wave Velocity (SWV). Biochemical tests included transaminase levels. 19 children with chronic liver disease underwent biopsies. SWV was measured globally and separately for the liver-segments 1 and 8. Correlations between the SWV and laboratory test were established using non-parametric Spearman correlation test.

Results: A total of 103 children underwent liver ultrasound elastographic assessments. Of these, 39 had malignancies, 19 had various chronic liver diseases, 13 had nonalcoholic fatty liver disease (NAFLD), and 32 were healthy controls. The transaminase values differed significantly between children with liver diseases and controls. In normal controls SWV values in the 1st segment were significantly lower compared to those in the 8th segment of the liver ($p = 0.0216$). In the group with hepatic steatosis, the SWV values were statistically higher compared to those in healthy controls. Positive statistical correlations have been established between AST and SWV in the group of children with NAFLD and those with malignancies ($p = 0.0032$, $p = 0.0045$).

Conclusions: Quantification of liver fibrosis by ARFI method correlates with the histological fibrosis stage in children with chronic liver disease and NAFLD. Clinical applications of this method in the diagnosis of pediatric liver disease deserve further study.

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1. Background

Chronic liver diseases such as nonalcoholic fatty liver disease (NAFLD), hepatotoxicity due to drugs and liver involvement in various childhood malignancies represents emerging public health problems in the pediatric population [1]. Regardless of its cause,

the common pathway of injury in chronic liver disease is fibrosis with the eventual development of the cirrhotic syndrome.

Although important information can be obtained from clinical symptoms of liver damage (fatigue, anorexia, nausea, vomiting, jaundice, pruritus), abnormalities in laboratory tests (elevations in bilirubin, gamma-glutamyl transpeptidase – (GGT), alkaline phosphatase – (AF), hypoalbuminemia), abdominal ultrasonography including Doppler assessments of portal vein flow direction as well as magnetic resonance imaging (MRI), the amount of hepatic fibrosis seen on hepatic biopsy specimens represents the gold standard for the assessment of the degree of chronic liver damage. The invasive nature of this procedure, in addition to its potential risks, contributes to its poor acceptability by children and parents alike [2,3].

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Therefore, great interest is expressed nowadays in finding a non-invasive method of the degree of liver fibrosis as an alternative to hepatic biopsy [4]. Conventional ultrasonography is usually the first-line investigation due to its low cost, non-invasive nature, reproducibility and relatively easy access. In developing countries, MRI and positron emission computed tomography (PET-CT), are very costly and restricted to selected cases due to their limited availability, while computed tomography (CT) is avoided in children due to concerns for radiation exposure in this population. The availability of new imaging technology that could increase US sensitivity for detection of hepatic fibrosis would therefore represent a major advancement in this field [4].

Elastography is a novel non-invasive method using focused ultrasound (US) as a source of mechanical excitation and generating images based on tissue response to this localized excitation [5,6]. Acoustic Radiation Force Impulse Imaging (ARFI) is a novel technique based on the generation of an acoustic impulse in the tissue in order to assess/interrogate the mechanical properties of the tissue (i.e. stiffness/elasticity) [6]. ARFI technology involves a mechanical compression of the tissue using acoustic impulses for a short time (pushing impulses), in a region of interest chosen by the examiner, which produces shear waves that spread from the interest area, perpendicularly on the acoustic impulse, generating localized displacements in the tissue, with a size of several microns [5]. At the same time, detection waves of smaller intensity than the pushing impulse are generated (1:100). The moment of interaction between the shear waves and the detecting waves marks a short period between the shear waves 'generation and the waves' crossing of the region of interest [5]. This shear wave velocity can be quantified (SWV) (m/s) by recording the position of the shear waves in many locations and correlating these measurements with the time period, generally, the stiffer the region of the tissue is, the greater the speed of the shear wave which passes through that region [6]. Thus, the measured SWV is an intrinsic feature measured by an intrinsic and reproducible feature of the tissue [5,7]. The equipment measures SWV as well as the depth where the measurement was performed [6]. Through supplementary software control algorithms and imagery detection, the ARFI method can simultaneously offer B-mode recording, color Doppler and ARFI images [8]. By eliminating the need of examiner compression on the tissue, characteristic of previously available elastography methods, ARFI eliminates a potential source of operator based variability in measurements and can evaluate tissue elasticity at deeper levels (up to 8 cm depth) [4,9–12].

In adults, Acoustic Radiation Force-Based Imaging (ARFI) modalities have been used to non-invasively characterize various tissues such as liver, kidney, lymph nodes, spleen, breast without the need for a biopsy [3,13,14]. In adult liver disease, ARFI elastography allows valid, accurate and flexible evaluation of liver stiffness [14]. Elastography of the left liver lobe is also possible, which may be especially helpful in obese patients [5,15]. However, the use of this technology in children has not been widely reported. Several small communications regarding its effectiveness, sensitivity and specificity in quantifying liver fibrosis in pediatric populations have been made at several conferences [6,16]. Few studies on children and rather poor data on childhood pathology, the latter referring in particular to transient elastography [17].

Our study aimed to assess the performance of real-time elastography using ARFI technology in evaluating the degree of fibrosis in children with various etiologies of liver disease such as non-alcoholic fatty liver disease (NAFLD) in the setting of obesity, liver disease in the setting of various solid and hematological disorders liver injury in the context of other diseases, in comparison with a group of healthy children.

2. Methods

Consecutive children aged between 1 and 18 years hospitalized in the 1st Pediatrics Clinic Tg. Mures between September 15, 2010 and January 15, 2011 were eligible for the study. The following groups were recruited: healthy controls (group 1); children with various chronic liver diseases (group 2), overweight or obese children with NAFLD (group 3), and children with early solid or hematological malignancies (group 4). The latter group included children in with early stages of disease, before during and after chemotherapy, respectively. Children without any changes of liver Eco structure on the baseline conventional ultrasonography in the 2B mode, normal transaminases, AF, lactate dehydrogenase (LDH) and prothrombin index (PI) were included in the control group. Children with chronic viral hepatitis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, Wilson's disease, hepatomegaly of other etiology, were included in group of children with chronic liver disease. Those with BMI-for-age between the 85th and 95th percentiles (overweight), and those above the 95th percentile (obese) according to World Health Organization standards, with hepatic enzyme abnormalities or conventional ultrasound appearance consistent with NAFLD were included in the group of children with overweight/obesity and NAFLD. Children with acute lymphoblastic and acute myeloblastic leukemias, neuroblastomas, lymphomas and myelodysplastic syndromes were included in the group of children with malignancies. Patients with ascites, human immunodeficiency virus (HIV) co infection, any infectious diseases other than hepatitis virus infection were excluded.

All study patients had the following laboratory tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), total cholesterol, triglycerides, total bilirubin and its' direct and indirect fractions. Height (kg) and weight (cm) were used to calculate the Body Mass Index (kg/m^2) (BMI). Medium Upper Arm Circumference (MUAC) was measured at the mid-point between the tips of the shoulder and elbow, using a tape measure calibrated in centimeters and Tricipital Skin Fold (TSF) was measured in the posterior upper arm, using a thickness caliper, as additional surrogate measures for nutritional status.

A single examiner performed US elastography using ARFI in all patients in the supine position with the right arm raised over the head. The elastography examination was performed with an ultrasound machine Siemens S 2000, equipped with a transducer of 4.1 MHz. Virtual Touch (VT) tissue quantification technology (Siemens) was used for fibrosis quantification. SWV (m/s) was measured globally and then separately for the liver-segments 8 and 1 in the right and left lobes, respectively, in order to comparatively evaluate the elasticity in the right versus the caudate liver lobe [3]. In the caudate lobe, we assessed the elasticity in the 1st segment, given its independent blood supply and importance in pediatric liver transplantation [3]. All measurements were performed at a depth of 4 cm below the skin and 2.5–4.5 cm below the liver capsule (a perfect area for SVW measurement). The liver capsule was purposefully avoided as it is rich in fibrous tissue and could introduce bias. A total of 10 SVW measurements were made at each site and the median velocity values in that region were used for all statistical analyses. Liver biopsy was performed in all children with chronic liver diseases (group 2). For comparisons between histological staging of fibrosis and fibrosis staging by SWV, the latter was defined based on data on adults: $1.31 \pm 0.48 \text{ m/s}$ – no fibrosis, $1.52 \pm 1.02 \text{ m/s}$ – grade 1 fibrosis, $1.61 \pm 0.68 \text{ m/s}$ – grade 2 fibrosis, $1.76 \pm 0.76 \text{ m/s}$ – grade 3 fibrosis, $2.81 \pm 0.71 \text{ m/s}$ – grade 4 fibrosis.

2.1. Statistical analysis

Continuous variables were expressed as median $\pm$ standard error of mean (SEM) or standard deviation (SD – standard

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