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Use of magnetic resonance elastography to assess hepatic fibrosis in children with chronic liver disease

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Abstract

Management of pediatric chronic liver disease is limited by lack of validated noninvasive biomarkers of histological severity. We demonstrate that magnetic resonance elastography (MRE) is feasible and accurate in detecting significant hepatic fibrosis in a case series of 35 children with chronic liver disease, including severely obese children.

Keywords

nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; noninvasive biomarker; pediatric liver disease

The management of chronic liver diseases in children is impeded by lack of validated noninvasive biomarkers of histological severity, necessitating invasive and costly liver biopsies. An accurate noninvasive method to detect significant liver fibrosis would reduce dependence on liver biopsies, facilitate the conduct of pediatric randomized clinical trials and improve the ability to track clinical outcomes. Magnetic resonance elastography (MRE) has been shown to accurately detect significant hepatic fibrosis in adults,^{1,2} but feasibility of MRE and thresholds for detecting hepatic fibrosis in children are unknown. The aim of this pilot study was to evaluate the accuracy of MRE in detecting hepatic fibrosis in children. We hypothesized that MRE would have good accuracy (AUROC >0.90) for detecting significant degrees of fibrosis (stage ≥ 2) in a cohort of children and adolescents with chronic liver disease.

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The other authors declare no conflicts of interest.

Methods

This case series included 35 children and adolescents, ages 4 to 20 years, who were evaluated with MRE and liver biopsy as part of their clinical evaluation for chronic liver disease at Cincinnati Children's Hospital Medical Center from August 2011 to December 2012 [median 1.5 months (interquartile range or IQR: -0.5,4) between scan and biopsy]. Histological and MRE analyses were blinded to radiology and pathology data, respectively. The Institutional Review Board approved this study.

The histological diagnosis and staging of liver disease was performed on hematoxylin & eosin and Masson trichrome-stained slides. Fibrosis was staged as stage 0 = no fibrosis, stage 1 = portal/periportal or perisinusoidal, stage 2 = portal/periportal and perisinusoidal, stage 3 = bridging fibrosis, and stage 4 = cirrhosis. In subjects with NAFLD, a diagnosis of "definite NASH", "borderline NASH" or "not NASH" was determined based on overall histopathological pattern of injury.³

MRE was performed as previously described on a 1.5 Tesla GE HDx MRI scanner (General Electric Healthcare, Waukesha, Wisconsin, USA) with an active-passive driver system at 60Hz.⁴ Four axial slices through the broadest portion of the liver were obtained to generate shear wave images. Data were transferred to a post-processing workstation to generate quantitative stiffness maps (elastograms) and to manually draw regions of interest (ROI) to obtain mean shear stiffness values in kilopascals (kPa).

Logistic regression (SAS version 9.3) was used to evaluate the ability of log transformed mean kPa to predict significant fibrosis (stage ≥ 2) vs. minimal or no fibrosis (stage < 2)⁵ and determine AUROC.

Results

Median age of the 35 subjects was 13 years (IQR:12,16); 51% were male; 80% were white, 6% black and 14% other race; 14% were Hispanic. Median body mass index (BMI) was 33.9 kg/m² (IQR: 28.9, 38.2) with median BMI percentile of 99.2. Only one subject (age 4) required sedation; none experienced adverse events.

Twenty-two of the 27 subjects with NAFLD had borderline or definite NASH. The remaining 8 subjects had progressive familial intrahepatic cholestasis type 2, glycogenic hepatopathy related to Type 1 diabetes, autoimmune sclerosing cholangitis, Wilson disease, alpha 1 antitrypsin deficiency, portal venous cavernous transformation and thrombosis, transfusion hemosiderosis and a normal liver biopsy (in a patient with obesity and hepatomegaly). On histological staging, 27 subjects had minimal or no fibrosis: 11 with stage 1 and 16 with stage 0. Eight subjects had significant fibrosis: four with stage 2, three with stage 3 and one with stage 4.

Representative images demonstrate increasing liver stiffness corresponding with advancing stages of fibrosis (Figure 1). A cut-off of 2.71 kPa provided maximal sensitivity (88%) and specificity (85%) for detecting significant fibrosis with an AUROC of 0.92 (95% CI, 0.79-1.00; p = 0.02) (Figure 2).

Discussion

Imaging modalities that measure stiffness as a surrogate of liver fibrosis include MRE and two ultrasound-based (US) techniques, transient elastography (TE) and acoustic radiation force imaging (ARFI) elastography. TE demonstrated high accuracy [AUROC 0.99 (90% CI, 0.92-0.99)] in predicting significant fibrosis (stage ≥ 2) in a cohort of 52 Italian children

with NASH (mean age 13.6 ± 2.4 years).⁵ ARFI elastography has also demonstrated greater liver tissue stiffness in children with chronic liver disease including NAFLD (AUROC of 0.834, 0.818 and 0.983 for fibrosis stage F 1, F 2 and F=4 respectively).^{8,9}

However, obesity is associated with significantly higher technical failure rates for TE and ARFI elastography.⁶ Although TE was feasible in 96% of children in the Italian study, the cohort appears to be significantly less obese than NAFLD cohorts reported in the United States.⁵ Directly comparing obesity severity is complicated by potentially different population growth curves in Italy and the United States, however the mean BMI range was 24-27 kg/m² across fibrosis groups in the Italian study. This contrasts with the markedly higher BMI range in our cohort and the mean BMI of 34 kg/m² in children ages 8 to 17 years with biopsy-confirmed NAFLD in a multicenter clinical trial in the United States.⁷ The feasibility and reliability of US-based elastography in severely obese patients has not been studied.

MRE in contrast is less susceptible to technical interference from excess abdominal adiposity and interrogates a larger liver volume. In adults, MRE also has significantly greater AUROC for detection of fibrosis [0.994 for stage 2, 0.985 for stage 3, 0.998 for stage 4] compared with TE [0.837 for stage 2, 0.906 for stage 3, 0.930 for stage 4 for TE, $p < 0.05$].^{1,2}

Our study demonstrates that MRE has high accuracy to detect significant hepatic fibrosis in children with chronic liver disease, including severely obese patients. Our broader clinical experience to date with hepatic MRE has included over 100 children (including patients who have not had liver biopsies). Of these, only 2 subjects failed completion (one with BMI of 51.3 kg/m² with girth exceeding MRI bore diameter and one with weight >350 pounds). Given the large proportion of severely obese pediatric patients with NAFLD in the United States, MRE may be particularly advantageous in the evaluation of NAFLD.⁷ An added strength of MR methodology is the ability to more precisely measure liver fat which also allows noninvasively determining steatosis outcomes.^{10,11} To reduce expense, MRE is performed at our institution as part of a limited liver MR examination which reduces cost to about twice that of abdominal US.

In summary, our data illustrate that MRE holds great promise to noninvasively detect fibrosis severity in pediatric liver disease, which could reduce dependence on liver biopsies which can be misclassified due to sampling error, insufficient liver biopsy size or fragmentation.¹² Our study is limited by small sample size inherent to a pilot study of feasibility. Larger prospective studies in children with chronic liver disease should be pursued to validate this novel technology.

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Abbreviations

MRE	magnetic resonance elastography
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
ROI	region of interest
US	ultrasound
TE	transient elastography
ARFI	acoustic radiation force imaging
IQR	interquartile range

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Figure 1.

Representative axial MRE images from three subjects. (A) 9 year old female, BMI 33.4 kg/m², with NASH and stage 1c fibrosis. The elastogram demonstrates a hepatic ROI with mean liver stiffness value of 2.2 kPa (blue-purple colors indicate low liver stiffness). The software algorithm automatically excludes the cross-hatched regions secondary to insufficient wave penetration. (B) 12 year old male, BMI 38.6 kg/m², with NASH and stage 3 fibrosis. The hepatic ROI has a mean liver stiffness value of 3.6 kPa (yellow and orange colors indicate elevated liver stiffness). (C) 15 year old female, BMI 22 kg/m², with autoimmune sclerosing cholangitis and cirrhosis. The hepatic ROI has a mean liver stiffness value of 4.9 kPa (prominent yellow, orange and red colors indicate markedly elevated liver stiffness).

Figure 2.
AUROC for MRE discrimination between stage 2 vs. stage 0-1 fibrosis.