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ORIGINAL ARTICLE

Evaluation of liver fibrosis with T2 relaxation time in infants with cholestasis: comparison with normal controls

Mi-Jung Lee · Myung-Joon Kim · Choon-Sik Yoon · Seok Joo Han · Young Nyun Park

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Abstract
Background The degree of hepatic fibrosis in biliary atresia (BA) correlates with the prognosis of the disease and thus, early diagnosis of liver fibrosis is clinically important. Liver biopsy is the gold standard for the evaluation of liver fibrosis, but it is an invasive procedure requiring sedation in children. Therefore, it is desirable to identify a noninvasive method for diagnosis and follow-up of hepatic fibrosis.
Objective The purpose of this study is to evaluate the possibility of quantifying liver fibrosis in infants by T2 relaxation time measurements.
Materials and methods The institutional review board approved this prospective study and parental informed consent was obtained. During MR cholangiopancreatography using a 1.5-T MR scanner in infants with neonatal cholestasis, T2 relaxation time of the liver was calculated with the mean signal intensities measured on images obtained using spin-echo sequences (TR/TE, 2,000/20, 40, 60, 80, 100, 120, 140, 160 ms). A normal control study was performed during spinal MRI in infants with anorectal malformation and normal liver enzyme profiles. A liver biopsy was obtained in the children with cholestasis. The correlation between histopathological fibrosis stage and T2 relaxation time was evaluated by Kendall's Tau-b test.
Results Twenty-five infants (male: female, 12:13; age range 0–11 months, mean 3.2 months), 14 with neonatal cholestasis (9 BA and 5 non-BA) and 11 normal controls were included in this study. Relaxation times (mean± standard deviation [SD]) for the liver were 57.8 ms±8.8 in the normal control group (n=11) and 56.8 ms±9.6 in the BA group (n=9) without statistically significant differences (P=0.811). T2 relaxation times were not significantly different between the low stage (≤F1) and high stage (≥F2) fibrosis (mean 57.8 vs 56.8; P=0.934).
Conclusion T2 relaxation of a normal infant liver at 1.5-T had a mean value of 57.8 ms, which is comparable with adult data (46–57 ms). However, T2 relaxation time was not different in patients with BA and did not correlate with stage of fibrosis.

Keywords Liver · Fibrosis · MRI · Infant

C.-S. Yoon
Department of Radiology, Gangnam Severance Hospital,
Yonsei University, College of Medicine,
Seoul 135-720, South Korea

S. J. Han
Department of Pediatric Surgery, Severance Children's Hospital,
Yonsei University, College of Medicine,
Seoul 120-752, South Korea

Y. N. Park
Department of Pathology, Severance Hospital, Yonsei University,
College of Medicine,
Seoul 120-752, South Korea

M.-J. Lee · M.-J. Kim · S. J. Han · Y. N. Park
Severance Pediatric Liver Disease Research Group,
Seoul 120-752, South Korea

Present Address:
M.-J. Lee · M.-J. Kim (✉)
Department of Radiology and Research Institute of Radiological Science, Severance Children's Hospital, Yonsei University,
College of Medicine,
250 Seongsanno (134 Sinchon-dong),
Seodaemun-gu, Seoul 120-752, South Korea
e-mail: mjkim@yuhs.ac

Introduction

Liver fibrosis is due to excessive deposits of collagen, proteoglycans and other macromolecules in the extracellular matrix in response to repetitive liver injury from various causes. This fibrotic response can cause all the complications of end-stage liver disease, including portal hypertension,

ascites, encephalopathy, synthetic dysfunction and impaired metabolic capacity [1]. Originally considered irreversible, a marker of injury and a component of the wound healing mechanism, liver fibrosis is now regarded a dynamic process with potential for regression [2]. Thus, the staging of liver fibrosis is important for treatment planning and for prognosis. Biliary atresia (BA) is a progressive obliterative cholangiopathy that occurs in neonates and is an significant cause of chronic liver disease in children [3]. If untreated, progressive liver fibrosis and cirrhosis lead to death by age 2 [4]. BA is the most common cause of liver transplantation in children [5, 6]. Therefore, the staging of liver fibrosis in infants with BA is as important as it is in adults.

A liver biopsy is the standard of reference for diagnosing liver fibrosis. However, it is invasive and subject to complications and sampling variability. These limitations make it undesirable for diagnosis and monitoring. Thus, the development of a noninvasive, accurate and reproducible alternative would be of great value [7, 8].

There have been many reports on the measurement of liver fibrosis by MRI including T2 relaxation time calculation [9–12]. In patients with advanced cirrhosis, unenhanced MR imaging may depict fibrotic septa and bridges as high signal intensity reticulations on T2-weighted images [13]. These signal intensity characteristics can be explained in part by the high water content of advanced fibrosis, which gives it a prolonged T2 relaxation time [7]. Thus, this study aimed to evaluate the possibility of liver fibrosis quantification with T2 relaxation time measurements in infant livers, by comparing infants with BA and normal controls.

Materials and methods

Patients

The institutional review board at our hospital approved this prospective study and informed consent was obtained from the parents of each child. T2 relaxation time measurements were performed during MR cholangiopancreatography (MRCP) in infants with neonatal cholestasis. A normal control study was performed during spinal MRI in infants with anorectal malformation and normal liver enzyme profiles. Included liver enzymes were aspartate aminotransferase. (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin level. The normal limits of these enzymes were: serum AST 13—34 units/l, serum ALT 5–46 units/l, serum ALP 60–300 units/l and total bilirubin <1.2 mg/dl.

MR imaging

From May to October 2009, MRI was performed under deep sedation with intravenous injection of propofol (Diprivan; AstraZeneca, London, UK) at a dose of 2 mg/kg by anaesthestists in a 1.5-T MR scanner (Intera Achieva, Philips Medical Systems, Amsterdam, Netherlands) using a cardiac coil. T2 relaxation time of the liver was calculated after routine MRCP or spinal MRI with the mean signal intensities measured on images obtained by using spin-echo sequences (TR/TE, 2,000/20, 40, 60, 80, 100, 120, 140, 160 ms). The other imaging parameters were: 64×64 matrix, 20 cm field of view, slice thickness of 15 mm with 20-mm slice spacing, flip angle of 70° and bandwidth of 133.2 Hz/pixel. It took 2 min for each acquisition. The least square fitting was used to calculate the relaxation times.

Analysis

During image analysis, an operator-defined region-of-interest (ROI) measurement was performed in the right lobe of the liver in three different slices by one radiologist (Fig. 1). ROI was drawn as large as possible, but positioned to avoid major vessels. The target ROI size was 100 mm^2. The mean signal intensities were obtained by the sum of the value in three sites of the liver divided by three.

A liver biopsy was performed in the neonatal cholestasis group during operation or by US-guided biopsy. The pathological fibrosis staging was obtained with the META-

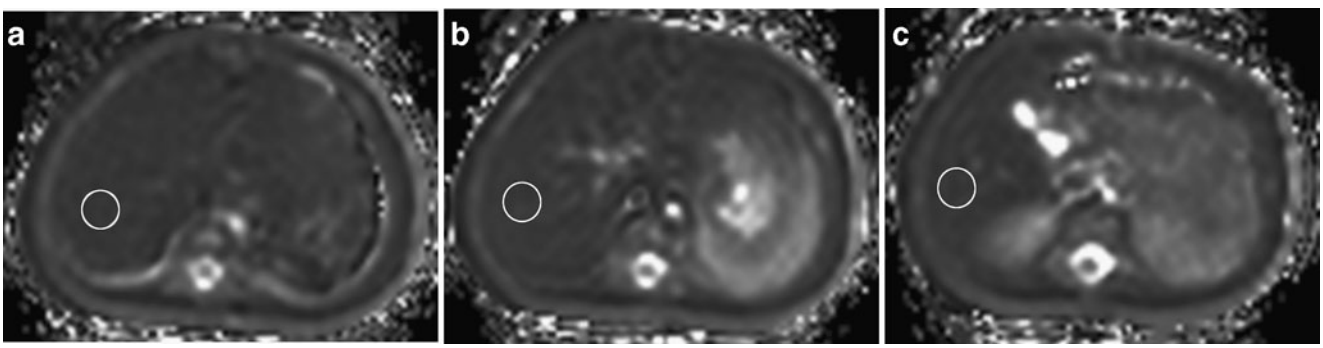


Fig. 1 Drawing ROIs in liver on MRI. Circular ROIs were drawn in three slices (**a, b, c**) within the right lobe of the liver, avoiding any major vessels

Table 1 Comparison between BA and normal control groups

	Normal (n=11)	BA (n=9)	P-value
Sex (M:F)	7:4	2:7	0.080*
Age (months)	5.0±3.3	2.0±1.3	0.031**
Fibrosis stage		2.9±0.9	
T2 (ms)	57.8±8.8	56.8±9.6	0.811**

* from Fisher exact test, ** from Mann–Whitney U test

VIR system [14]. In this, fibrosis is categorized into five stages: no fibrosis (F0), portal fibrosis (F1), periportal fibrosis (F2), septal fibrosis (F3) and cirrhosis (F4). A liver biopsy was not performed in the normal control group.

The correlation between the fibrosis stage and T2 relaxation time was evaluated. Statistical analysis was performed using statistical software (SPSS, version 17; SPSS, Chicago, IL, USA). Differences in the sex of each group were tested by using Fisher exact test. The Kruskal-Wallis test was used to evaluate the difference between patients and the control group and Kendall's Tau-b test to evaluate the correlation between METAVIR and T2. When comparing the age and T2 relaxation time between two groups, the Mann–Whitney U test was used. Statistically significant differences were defined as those with P values <0.05.

Results

Twenty-five infants were included. There were 12 boys and 13 girls with a mean age of 3.2 months (range 0–11 months). There were 14 infants with neonatal cholestasis and 11 normal controls. Final diagnoses were BA in nine cases and non-BA in five (including two neonatal hepatitis, one choledochal cyst, one total parenteral nutrition-induced cholestasis and one annular pancreas).

On histopathological staging, four non-BA cases showed no fibrosis. The remaining case of the non-BA group was one of a choledochal cyst and the fibrosis stage of this case was F1. BA cases showed high stage (>2) fibrosis (F2 in four cases, F3 in two cases and F4 in three cases).

The comparison of the BA and normal control groups is summarized in Table 1. The mean age was younger in the BA group than in the normal group (P=0.031). The mean fibrosis stage was 2.9 in the BA group. However, T2 relaxation times of the livers were not significantly different between the BA group and the normal controls (P=0.811) (Fig. 2). The mean T2 relaxation time of the normal infant livers was 57.8 ms.

In considering liver fibrosis, the mean T2 relaxation time of each fibrosis group is demonstrated in Table 2. The T2 relaxation times were not different between the different fibrosis groups (P=0.163 from Kruskal-Wallis test) and did not correlate with fibrosis stage (r=−0.034, P=0.87 from Kendall's Tau-b test) (Fig. 3). T2 relaxation times were not significantly different between the low stage (F0 or F1) and high stage (≥F2) fibrosis (mean: 57.8 vs 56.8; P=0.934) (Table 3).

Discussion

BA is an obliterative cholangiopathy that involves all or part of the biliary tree. Although selected patients benefit from prompt diagnosis and Kasai portoenterostomy surgical intervention within the first 60 days of life, many ultimately require liver transplantation because of portal hypertension, recurrent cholangitis and cirrhosis [3]. The degree of fibrosis correlates with the prognosis of the disease and thus, early diagnosis of liver fibrosis is clinically important [3, 15].

Liver biopsy is the gold standard for the evaluation of liver fibrosis, whilst imaging studies such as an MRI can be more costly than US-guided liver biopsy. However, liver biopsy is invasive and also requires deep sedation in infants and young children and is therefore not desirable for repeat follow-up. For these reasons, there are many studies regarding noninvasive imaging evaluation of liver fibrosis; however, most studies have been performed in adults. A recent review suggested several elasticity imaging techniques in children, including transient elastography, acoustic radiation force impulse

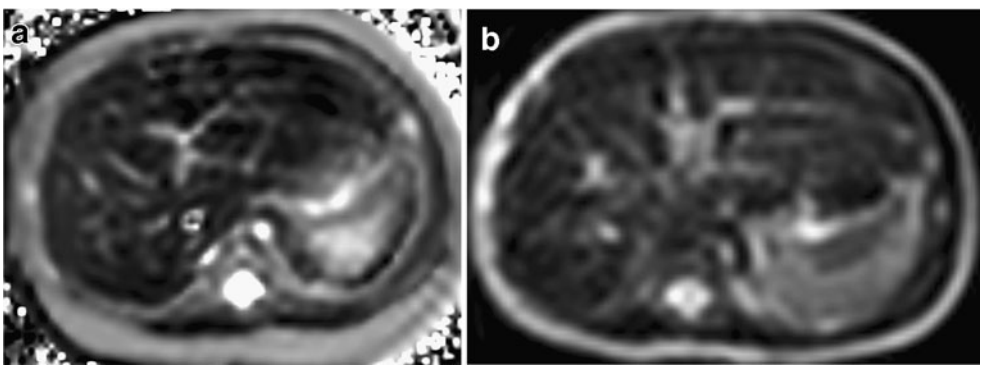


Fig. 2 Comparison of T2 relaxation time in the liver. **a** T2 relaxation time (52.1 ms) of a 2-month-old normal control boy. **b** T2 relaxation time (60.7 ms) of a 2-month-old girl with BA and secondary liver cirrhosis (F4)

Table 2 Mean T2 relaxation time of each fibrosis group

Fibrosis stage	Number of patients	Age (months)	T2 (ms)
F0	15	4.1±3.2	58.8±43.0
F1	1	1	43.0
F2	4	1.3±0.5	53.4±10.7
F3	2	1.5±0.7	51.4±8.2
F4	3	3.3±1.5	64.8±4.0
*P value		0.113	0.163

* from Kruskal-Wallis test

Table 3 Comparison between mild (≤F1) and severe (≥F2) fibrosis groups

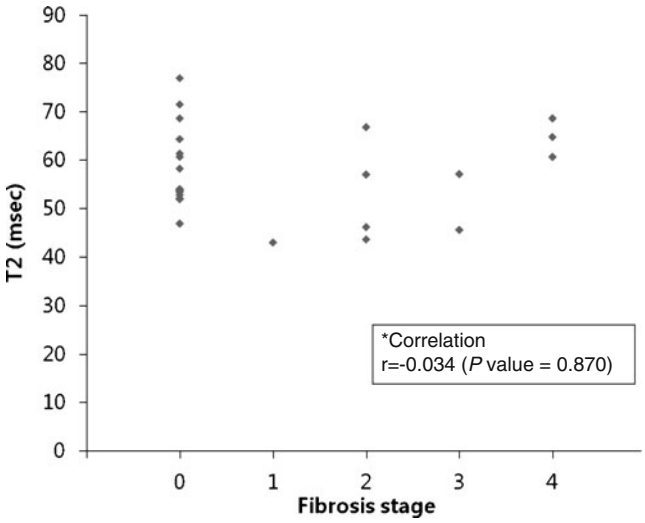
Fibrosis stage	≤F1 (n=16)	≥F2 (n=9)	P value
Sex (M:F)	10:6	2:7	0.063*
Age (months)	3.9±3.3	2.0±1.3	0.169**
Fibrosis stage	0.1±0.3	2.9±0.9	
T2 (ms)	57.8±9.1	56.8±9.6	0.934**

* from Fisher exact test, ** from Mann–Whitney U test

imaging, supersonic shear imaging, MR elastography and MR diffusion and perfusion imaging [16]. Menten et al. [17] reported the usefulness of transient elastography for the evaluation of hepatic fibrosis in patients with cystic fibrosis. However, there was no report about T2 relaxation time of the liver in infants.

The reported normal liver T2 relaxation time in adults on a 1.5-T MR scanner is 46–57 ms [18–20]. Some reports have shown an increase in T2 relaxation times in cases with liver fibrosis [11, 12]. Aube et al. [10] presented a high correlation between the area of fibrosis and T2 relaxation time (r=0.78, P<0.01) with rats and showed that fibrosis could be diagnosed with an accuracy of 100%. However, some authors showed no remarkable correlation between the relaxation times and the degree of tissue injury [21]. Our study also showed no significant correlation between liver fibrosis and T2 relaxation time in infants.

It is known that different histopathological changes are present in liver cirrhosis, including accumulation of connective tissue, inflammatory changes, fatty infiltration and iron accumulation. However, there are no reports discriminating the influence of these changes on relaxation times and signal intensities on liver MR images. Kreft et al. [9] also showed a good correlation between the liver T2 relaxation time and the amount of connective tissue in liver fibrosis and said that this probably results from the associated inflammatory changes rather than the increased amount of connective tissue.



*from Kendall's Tau-b test

Fig. 3 Scatter diagram of fibrosis stage and T2 relaxation time. T2 relaxation times did not correlate with fibrosis stage

These different histopathological changes are also present in BA with marked inflammatory progressive fibrosis. Guibaud et al. [22] suggested that MR imaging is able to show periportal fibrosis in BA, but with a lack of pathological correlation in their study. Therefore, the signal abnormality seen on MRI could be directly related to the inflammation (including oedema and vascular proliferation) rather than to the periportal fibrosis itself [23]. In our study, there was also combined inflammation and fibrosis in infants with neonatal cholestasis that might have influenced the T2 relaxation time of the liver. However, there was no significant difference of T2 relaxation time between the BA group and normal controls. We cannot explain this result based on histopathological fibrosis score alone. Further evaluation of liver T2 relaxation time measurement in the BA model with histopathological correlation is needed.

There are some limitations of our study. Firstly, the number of patients is small. There are a limited number of patients in each liver fibrosis stage (only one patient in F1, four in F2, two in F3 and three in F4). From this small number of patients we could not evaluate the difference between the T2 relaxation time of each liver fibrosis stage. Our study shows no significant difference of T2 relaxation time between the low-stage and high-stage liver fibrosis. Nevertheless, further evaluation of more patients with variable liver fibrosis stage is needed. The second limitation is that we included infants with anorectal malformation as a normal control group. Although the liver enzyme profiles were normal in these patients, a normal liver was not proven by pathology. In addition, we did not match age and gender between the neonatal cholestasis group and normal controls. The third limitation of this study is that we did not include the whole liver for measurement of T2 relaxation time. Size and placement of ROI can influence the signal measurements [24]. To reduce these influences,

the ROI was drawn by one radiologist in a similar location with a similar size in all patients in this study, so this should not invalidate our findings.

Conclusion

T2 relaxation time for normal infant liver at 1.5-T had a mean value of 57.8 ms, which is comparable with adult data (46–57 ms). However, T2 relaxation time was not different in patients with BA and did not correlate with hepatic fibrosis stage. T2 measurements are therefore unlikely to contribute to the clinical management of this patient group.

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