Diffusion-weighted Magnetic Resonance Imaging of the Liver in Hepatitis B Patients with Child-Pugh A Cirrhosis

Feng-O Hsu,[1] Yen-Yu Chiou,[1] Chiao-Yun Chen,[1,2] Gin-Chung Liu,[1,2] Hui-Chen Chu,[3] Hui-Cheng Liu,[3] Hui-Min Chu,[1] and Jui-Sheng Hsu[3,4]

[1]Department of Medical Imaging, Kaohsiung Medical University Hospital, [2]Department of Radiology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, [3]Department of Medical Imaging, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, and [4]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

The purpose of this study was to test the hypothesis that cirrhotic change of liver in hepatitis B patients observed in Child-Pugh classification based on clinical assessment would be reflected in the apparent diffusion coefficient (ADC) values calculated from diffusion-weighted magnetic resonance (MR) imaging. Twenty-seven patients with hepatitis B Child-Pugh class A cirrhosis and 10 control subjects were referred for measurement values of the liver on a 3.0-T MR unit. The results revealed that ADCs were significantly lower in hepatitis B patients with Child-Pugh class A compared with control subjects ($p < 0.01$). In conclusion, our preliminary study showed that hepatitis B patients with Child-Pugh class A had reduced ADC values in liver vis-a-vis normal subjects.

Key Words: diffusion-weighted imaging, hepatitis B, liver, magnetic resonance imaging
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Hepatitis B virus (HBV) infection is a common cause of liver disease throughout the world. Worldwide, it is estimated that there are 350 million people with persistent HBV infection. More than 75% of persistently infected people are in Asia, with an estimated 100 million in China; 12% and approximately 50 million are in Africa [1]. Around 15–20% of adults in Taiwan are chronically infected with HBV [2,3]. HBV infection can progress from an asymptomatic persistently infected status to chronic hepatitis B, cirrhosis and decompensated liver disease and/or hepatocellular carcinoma.

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Address correspondence and reprint requests to: Dr Jui-Sheng Hsu, Department of Medical Imaging, Kaohsiung Municipal Hsiao-Kang Hospital, 482 Shan-Ming Road, Kaohsiung 812, Taiwan.
E-mail: e3124@ms16.hinet.net

Liver biopsy is the most accurate means of assessing the stages of diffuse liver disease as early or advanced, pre-cirrhotic, and cirrhotic. However, liver biopsy is an invasive procedure with several contraindications and the risk of complications such as pain, hemorrhage, bile peritonitis, penetration of abdominal viscera, pneumothorax and death [4]. The mortality rate associated with needle biopsy has been estimated to be between 0.009% and 0.12% [4].

Cirrhosis can also be staged clinically. A reliable system is the Child-Pugh (CP) classification, which is based on a clinical (degree of ascites and hepatic encephalopathy) and laboratory assessment (values for albumin, prothrombin time and bilirubin). The CP classification can reasonably predict survival in many liver diseases and predicts the likelihood of major complications of cirrhosis such as bleeding from varices and spontaneous bacterial peritonitis [5].

Owing to the invasiveness of the biopsy procedure and its associated possible complications, the development of an alternative noninvasive method to characterize the condition of the liver is highly desirable. Diffusion is the thermally-induced motion of water molecules in biological tissues, also referred to as Brownian motion [6–8]. The microscopic motion includes molecular diffusion of water and microcirculation of blood in the capillary network (microperfusion). The clinical utility of diffusion-weighted imaging (DWI) of magnetic resonance has been established for acute stroke. Recently, DWI has also been applied to specific regions of the body to detect malignant lesions [9]. Several DWI applications have been reported showing that apparent diffusion coefficient (ADC) values vary in diffuse diseases such as cirrhosis and in focal lesions [9–11].

In this retrospective study, DWI was applied to hepatitis B patients and control subjects. The results were compared with the CP class in order to determine if this technique could be of diagnostic or prognostic value for hepatitis B.

Materials and Methods

The study protocol was approved by our institutional review board. Twenty-seven patients diagnosed with persistent hepatitis B (18 men, 9 women; age range, 23–84 years; mean age, 55.3 ± 16.1 years) and 10 control subjects (6 men, 4 women; mean age, 37.3 ± 8.4 years) were recruited for this study. Persistent hepatitis B was defined as the presence of hepatitis B surface antigen (HBsAg) in the serum for 6 months or longer. All hepatitis B patients were hepatitis C negative. Patients with focal malignant lesions of the liver visible on imaging procedures including ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) were excluded from the study. The CP classification is based on a scoring system of 5 to 15; scores of 5 and 6 are CP class A, scores of 7–9 indicate class B, and 10–15, class C [5]. Applying the CP scoring system to assess the severity of cirrhosis, all hepatitis B patients were classified as CP class A. Control subjects had no known liver disease.

MRI

Patients were examined with a 3.0-T superconducting MR system (GE Medical Systems, Milwaukee, WI, USA) with a standard body coil (GE Medical Systems). All patients underwent DWI with a routine hepatic MR protocol. The hepatic protocol included a T1-weighted spin-echo (130 ms/1.4 ms, repetition time [TR]/echo time [TE]; number of excitations [NEX], 1.0; 8 mm slice thickness; 40 cm × 40 cm field of view [FOV]; 256 × 128 matrix), a T1-weighted dual fast gradient-recalled-echo sequence (in-phase and out-of-phase sequences) (120 ms/2.1 ms, TR/TE [in-phase]; 120 ms/1.3 ms, TR/TE [out-of-phase]; flip angle, 60°; NEX, 1.0; 8 mm section thickness; 40 cm × 40 cm FOV; 256 × 128 matrix), and a T2-weighted fast spin-echo sequence with spectral fat saturation (2,000 ms/86 ms, TR/TE; NEX, 2.0; 8 mm section thickness; 40 cm × 40 cm FOV; 512 × 256 matrix). Two breath hold DWI sequences were performed with the single-shot echo-planar imaging technique with motion-probing gradients in three directions. The following parameters were used to acquire 20 sections in a 24-second breath hold (two b values: 0 and 500 s/mm^2; 1,000 ms/61.1 ms, TR/TE; NEX, 1.0; 8 mm section thickness; 40 cm × 40 cm FOV; 128 × 256 matrix) and a T1-weighted gradient-echo sequence (3.7 ms/0.908 ms, TR/TE; flip angle, 10°) after dynamic injection of 0.1 mmol per kilogram of body weight of gadopentetate dimeglumine through a power injector at a rate of 2 mL/sec.

Image analysis

Signal intensities (SI) were measured on the images recorded in a homogeneous circular area (diameter, 1 cm; area, 3.1416 cm^2) at the posterior inferior segment of the right hepatic lobe to avoid motion artifacts and artifacts from the great vessels. Quantitative ADC maps were derived automatically on a voxel-by-voxel basis by using commercially available software (Advantage Workstation 4.0; GE Medical Systems). The ADC was calculated with a linear regression analysis of the function

$$S = S_0 \cdot e^{-b \times ADC}$$

where S is the signal intensity after application of the diffusion gradient, b is the diffusion factor, and S_0 is the signal intensity at $b = 0$ sec/mm^2.

Signal to noise ratios (SNRs) of liver on DWI were calculated

$$SNR = S/SD_{noise}$$

where S is the signal intensity and SD_{noise} is the standard deviation of the background noise.

Statistical analysis

Differences between the two sets of data were assessed with Student's *t* test. A p value < 0.05 was considered significant.

Results

The SNRs of DWI and ADC for the liver are summarized in the Table. There was no significant difference in the SNRs of DWI between the control subjects and hepatitis B patients. For control subjects, the average ADC was $1.68 \pm 0.11 \times 10^{-3}$ mm^2/sec. For the hepatitis B patients with CP class A, it was $1.44 \pm 0.19 \times 10^{-3}$ mm^2/sec. The mean ADC value in hepatitis B patients with CP class A was significantly lower than that in the control subjects ($p < 0.01$).

Table. Signal to noise ratio (SNR) and apparent diffusion coefficient (ADC) values ($\times 10^{-3}$ mm^2/sec) measured in the liver of control subjects and hepatitis B patients with Child-Pugh class A liver cirrhosis*

	Control subjects ($n = 10$)	Hepatitis B patients ($n = 27$)	p
SNR	146.29 ± 25.87	155.98 ± 31.84	> 0.05
ADC	1.68 ± 0.11	1.44 ± 0.19	< 0.01

*Data are presented as mean ± standard deviation.

Discussion

Diffusion is the microscopic randomly translated motion of molecules, and water molecular diffusion can be measured *in vivo* using DWI and an ADC [8]. In many biological tissues, particularly those that have regular, ordered microstructure, the diffusion coefficient depends on the direction along which it is measured. MRI can only measure differences directionally, and dependent components must be measured separately. However, the liver, unlike the brain and kidney, has an isotropic diffusion pattern, probably due to its randomly organized structure [12]. This indicates that the use of multidirectional diffusion gradients is unnecessary in hepatic diffusion studies. In this study, we used DWI with motion-probing gradients in three directions.

The average ADC value calculated for control subjects in this study is in agreement with reported values of 1.52 to 1.79×10^{-3} mm^2/sec [10,13]. For the hepatitis B patients with CP class A, the average ADC value was significantly lower than that in the control subjects, which correlates with lower ADC values for liver cirrhosis [11,14,15]. This finding is attributable to the progressive accumulation of an extracellular fibrillary matrix (mainly type I and type II collagen), which characterizes chronic liver disease of any etiology and is most completely expressed in cirrhosis [16]. The deposit of collagen fibers "restricts" the motion of the water molecules and therefore reduces ADC values in cirrhotic liver.

Our study had some limitations. Firstly, the number of patients included in our study was relatively small. Secondly, we only enrolled patients with class A cirrhosis in our study instead of those with all classes of liver cirrhosis. Therefore, the results are only applicable to mildly severe cirrhotic patients. As for class B or class C cirrhotic patients, we are unable to draw conclusions as to whether or not the ADCs would be even lower than that of class A patients. The reason for why we did not recruit class B and class C patients was that in our institute, we did not have many patients with this condition. Third, high spatial resolution and less distortion are desirable for DWI of the liver. Single-shot echo-planar imaging DWI is limited in both features. Combining DWI with superparamagnetic iron oxide, fluid-attenuated inversion-recovery, and high-field and/or new developing sequences, such as multi-shot echo-planar imaging DWI and propeller DWI, would push DWI of the liver to the first-line imaging study in the near future [9]. Therefore, further study with a larger sample size and more variety of severity in cirrhotic patients will be needed to give a conclusive opinion for that question.

In summary, our preliminary study showed that hepatitis B patients with CP class A liver cirrhosis had lower ADC values than control subjects without any known liver disease. ADC measurement may have a good potential for correlation with CP classification of viral hepatitis B.

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B 型肝炎患者合併 Child-Pugh 分類 A 肝硬化的肝臟擴散磁振加權造影術之評估

許鳳娥[1] 邱燕玉[1] 陳巧雲[1,2] 劉金昌[1,2] 朱惠珍[3]
劉慧菁[3] 朱慧敏[1] 許瑞昇[3,4]
[1]高雄醫學大學附設醫院 影像醫學部
[2]高雄醫學大學 醫學院醫學系 放射線學科
[3]高雄市立小港醫院 影像醫學科
[4]高雄醫學大學 醫學研究所

本研究的目的為測試 B 型肝炎患者之 Child-Pugh 臨床肝硬化分類代表的肝臟硬化之變化會在擴散磁振加權造影術之擴散係數 (apparent diffusion coefficient、ADC) 表現出來的假說。27 位 Child-Pugh 分類 A 的 B 型肝炎患者與 10 位沒有肝臟疾病的控制組接受 3.0-T 磁振造影儀肝臟擴散磁振加權造影術。就肝臟擴散係數加以比較。結果發現 Child-Pugh 分類 A 的 B 型肝炎患者的肝臟擴散係數明顯低於控制組 ($p < 0.01$)。我們初步的結果顯示 B 型肝炎合併 Child-Pugh 臨床肝硬化分類 A 之患者會使肝臟擴散係數降低。

關鍵詞：擴散磁振加權造影術，B 型肝炎，肝臟，磁振造影術
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通訊作者：許瑞昇醫師
高雄市立小港醫院影像醫學科
高雄市812小港區山明路482號