Assessment of Activity of Crohn Disease by Diffusion-Weighted Magnetic Resonance Imaging

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INTRODUCTION

Crohn disease (CD) is a chronic and relapsing inflammatory disorder of the gastrointestinal tract. Accurate evaluation of disease activity is crucial for treatment planning. The evaluation is currently based on a combination of clinical score, such as Crohn disease activity index (CDAI), laboratory indexes, endoscopic, and histologic findings.1,2 Crohn disease activity index is subjective analysis of symptoms and is commonly used as the reference standard for management. Recently, MR enterography (MRE) is recommended as a new diagnostic tool in the management of CD.1,3 The lack of ionizing radiation and superior soft tissue resolution are especially beneficial for young patients who require serial examinations. MR enterography not only displays the morphologic changes, but also provides the functional information about the bowel wall. Diffusion-weighted imaging (DWI) has recently been investigated for assessing bowel wall in CD.3–7 It provides information about the random motion of extracellular water molecules in vivo. The apparent diffusion coefficients (ADCs) allow quantitative analysis of the diffusion characteristics of tissues. Reduced diffusion has been reported in inflamed bowel segments with active CD. Diffusion-weighted imaging was superior to contrast-enhanced magnetic resonance imaging (MRI) for detection of bowel inflammation.5,8–10 The purpose of this study was to assess the efficacy of DWI for evaluating activity of CD.

MATERIALS AND METHODS

Patients

Between August 2013 and February 2015, 92 consecutive patients with abdominal pain underwent MRE in our institution. A total of 45 patients were excluded because of a final diagnosis other than CD. A total of 47 patients (29 men, 18 women; mean age: 27.9 years; range: 11–57 years) with CD confirmed by standard clinical, endoscopic, and histologic criteria were enrolled in this prospective study. The median course of disease was of 30 months (range: 3–144 months). Thirty patients received oral corticosteroid, anti-inflammatory, and/or anti-TNF-α treatments, the other 17 patients had not received treatment at the time of initial diagnosis. Crohn disease activity index served for clinical activity scoring was tested within 1 week of MRE. Inactive disease was defined as a CDAI <150 and active disease was defined as a CDAI ≥150.11 The study was approved by the Institutional Ethics Review Board of the first affiliated hospital of Sun Yat-Sen University and written informed consent was obtained from all patients.

Magnetic Resonance Enterography Protocol

Bowel preparation included fasting for 6 to 8 hours and oral polyethylene glycol electrolyte solution. The patients ingested 1600 to 2000 mL of 2.5% mannitol solution as oral contrast...
1 hour before MRE. A total of 10 mg of racanisodamine hydrochloride (Minsheng Pharmaceutical Group Co., Ltd., Hangzhou, China) was slowly injected intramuscularly into the buttocks to induce gastrointestinal hypotonia 10 minutes before MRE. The examinations of the abdomen and pelvis were performed using a 3T magnetic resonance system (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany) and multichannel phased-array body coils. In addition to axial and coronal breath-held half-Fourier acquisition single-shot turbo spin-echo T2-weighted (HASTE-T2WI, repetition time: 1200 ms, echo time: 87 ms, 320 × 194 matrix, 4 mm slice thickness, 160° flip angle) and fat-suppressed fast low-angle shot T1-weighted (FS-FLASH-T1WI, 210/2.18 ms, 320 × 200, 4 mm, 70°) images, axial, and coronal free-breathing DWI was acquired with water-excited single-shot spin-echo echo-planar sequence (5000–5900/73–83 ms, 192 × 115, or 192 × 154, 4–5 mm) using 3 b values of 50, 400, and 800 s/mm². Apparent diffusion coefficients map was generated by using monoexponential model on the scanner console. After intravenous injection of 0.2 mL/kg gadolinium ethoxybenzyl diethylene-triaminepenta-acetic acid (Gadopentetate dimeglumine, BeiLi Pharmaceuticals, Beijing, China) at a rate of 2 mL/s, coronal dynamic contrast-enhanced fat-suppressed three-dimensional volumetric interpolated breath-hold examination (3D-VIBE, 4.37/1.37 ms, 320 × 217, 2 mm, 13°) was performed at 15 to 35, 40 to 60, 65 to 85, and 90 to 110 s from the beginning of injection.

**Magnetic Resonance Imaging Analysis**

The examinations were assessed qualitatively in consensus by 2 abdominal radiologists (C-HS and X-HL), who were blinded to clinical, laboratory, and endoscopic results. On MRE images, bowel wall thickness >3 mm or increased contrast enhancement was considered pathologic. The intestinal segments with most marked abnormalities were selected for evaluation of activity of CD including thickness, T2 signal intensity, and enhancement of bowel wall. Mural thickness greater than normal bowel wall (score 0) was scored 1 if the thickness >3 to 5 mm, 2 if >5 to 7 mm, and 3 if >7 mm. Mural enhancement greater than adjacent normal bowel wall (score 0) was scored 1 if the signal intensity was markedly less than arteries, 2 if slightly less, and 3 if equal to arteries in the arterial phase. The mural T2 signal intensity was scored 0 for normal, 1 for dark grey, 2 for light grey, and 3 for grey–white intensities. On DWI using b value of 800 s/mm², the mural hyperintensities greater than adjacent normal bowel wall (score 0) were scored 1 if they were lower than that of renal cortex, 2 if they were between that of renal cortex and spleen, and 3 if they were similar to or higher than that of spleen (Figure 1). The MRE score was defined as the sum of scores derived from the 3 conventional MRE findings. The MRE + DWI score was defined as the sum of scores derived from MRE score and DWI score.

On the automatically generated ADC maps, 1 radiologist (X-HL) calculated the mean ADCs by manually placing 3 round regions of interest (ROIs) on the areas of thickened bowel wall corresponding to highest signal intensities on DWI without including the intestinal content (Figure 2). The ADCs of the adjacent normal intestinal wall were obtained using the same method. The mean area of the ROI was 12.60 ± 2.60 mm².

**Statistical Analysis**

Data were analyzed using statistical software package (SPSS version 13.0; SPSS Inc., Chicago, IL). Apparent diffusion coefficients of the inflamed and normal bowel wall were compared using the paired-samples t test. Apparent diffusion coefficients in inflamed segments of active and inactive CD were compared using 2 independent samples t test. Diffusion-weighted MR imaging scores of active and inactive CD were compared using Wilcoxon rank sum test. The associations between MRE scores, MRE + DWI scores, and CDAI were evaluated with Spearman rank correlation analysis. The association between ADCs and CDAI was determined using Pearson correlation analysis. The areas under the receiver-operating characteristic (ROC) curves [areas under the receiver-operating characteristics curve (AUCs)] were calculated to determine the diagnostic accuracy of the imaging features, ADCs, and total MRE scores. Interobserver agreement for qualitative parameters
was performed with kappa statistics (kappa value ≥0.75 was defined as good agreement). All statistical tests were performed 2-sided with significance defined at \( P < 0.05 \).

**RESULTS**

**Clinical and Magnetic Resonance Enterography Findings**

The mean CDAI was 166.93 ± 100.89 (range: 22–380) with CDAI < 150 in 22 patients and CDAI ≥150 in 25 patients. The evaluated disease location was ileal or colonic, respectively, in 26 and 21 patients. The bowel segments enrolled in this study were all well distended. The MRE findings with corresponding scores in active and inactive CD were summarized in Table 1. In summary, low scores (score 1–2) were more observed in inactive CD whereas high scores (score 3–4) were more observed in active CD for each MRE findings.

The scores of DWI signal intensity in active CD (median: 3; range: 1–3) were significantly greater than that of inactive CD (median: 1; range: 0–2; \( P < 0.001 \)). The scores of MRE findings in active and inactive CD were shown in Figure 3. The MRE + DWI scores in active CD (median: 9; range: 3–12) were significantly greater than that of inactive CD (median: 5; range: 0–7; \( P < 0.001 \)). The median of MRE scores in 47 patients was 5 with a range of 0 to 9. Good interobserver agreements were obtained for DWI signal intensity (\( K = 0.76, P < 0.001 \)) and enhancement scores (\( K = 0.78, P < 0.001 \)), followed by scores of T2 signal intensity (\( K = 0.63, P < 0.001 \)).

**TABLE 1.** Magnetic Resonance Enterography Findings in Active (n = 25) and Inactive (n = 22) Crohn Disease Patients

| Score                          | Inactive | Active | Inactive | Active | Inactive | Active | Inactive | Active | Inactive | Active |
|-------------------------------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|
| Mural thickening              | (≤3 mm)  | 6      | 2        | (>3–5 mm) | 10      | 1      | (>5–7 mm) | 3      | 4        | (>7 mm) | 3      | 18     |
| Mural T2 signal intensity     | (Normal) | 10     | 2        | (Mild)  | 9       | 9      | (Moderate) | 3      | 5        | (Marked) | 0      | 9      |
| Mural enhancement             | (Normal) | 3      | 2        | (Mild)  | 13      | 7      | (Moderate) | 3      | 8        | (Marked) | 3      | 8      |
| DWI \( (b = 800 \text{s/mm}^2) \) signal intensity | (Normal) | 7      | 0        | (Mild)  | 6       | 2      | (Moderate) | 9      | 6        | (Marked) | 0      | 17     |

DWI = diffusion-weighted MR imaging.
In 47 patients, the ADCs in inflamed segments ($1.28 \pm 0.47 \times 10^{-3}$ mm$^2$/s) were significantly lower than that of normal bowel wall ($2.09 \pm 0.27 \times 10^{-3}$ mm$^2$/s; $P < 0.001$). The ADCs in inflamed segments of active CD ($0.92 \pm 0.18 \times 10^{-3}$ mm$^2$/s) were significantly lower than that of inactive CD ($1.68 \pm 0.36 \times 10^{-3}$ mm$^2$/s; $P < 0.001$).

**Correlation Analysis**

Bivariate correlation indicated a significant positive correlation between the DWI scores and CDAI ($r = 0.74$, $P < 0.001$). There was a significant negative correlation ($r = -0.71$, $P < 0.001$) between ADCs in inflamed segments and CDAI (Figure 4), and no significant correlation ($r = 0.27$, $P = 0.174$) was found between ADCs in normal segments and CDAI. There was significant positive correlation between MRE scores and CDAI ($r = 0.54$, $P < 0.001$) as well as between MRE + DWI scores and CDAI ($r = 0.66$, $P < 0.001$).

**RECEIVER-OPERATING CHARACTERISTIC ANALYSIS**

Receiver-operating characteristic analysis (Figure 5) showed higher diagnostic accuracy of DWI hyperintensity with AUC of 0.90 ($P < 0.001$) for CD activity than that of bowel wall thickness (AUC = 0.83, $P < 0.001$), T2 hyperintensity (AUC = 0.80, $P < 0.001$), and contrast enhancement (AUC = 0.68, $P < 0.001$). The AUC of ADCs in inflamed segments was significantly higher at 0.98 ($P < 0.001$) with 100% sensitivity and 88% specificity for diagnosing active CD using a threshold ADC value of $1.17 \times 10^{-3}$ mm$^2$/s. The AUC of MRE + DWI scores (0.88) was slightly higher than that of MRE scores (0.83) without statistical significance ($P = 0.448$; Figure 6).

**DISCUSSION**

Diffusion-weighted MR imaging has been used for assessment of activity of CD.\cite{12,13} We also found that the bowel segments of active CD had more markedly reduced diffusion with hyperintensity on high b value DWI and low ADCs than that of inactive CD. The mechanism for the restricted diffusion of water molecules may reduce extracellular space from increased cell density and viscosity, granuloma formation, and dilated lymphatic channels.\cite{5} Qualitative assessment of the bowel wall signal intensity on DWI correlated positively with CDAI, whereas the ADCs correlated inversely with CDAI in our study. No similar correlation was found between ADCs in normal bowel segments and CDAI. The ADCs measured from inflamed bowel wall were significantly lower than normal bowel wall. Diffusion-weighted MR imaging signal intensities increased and ADCs decreased with increasing activity of CD. Receiver-operating characteristics analysis showed higher AUC of DWI using b value of 800 s/mm$^2$ than that of conventional MRE findings (mural thickness, T2 signal intensities, and enhancement), and ADCs had high AUC of 0.98 for differentiating active from inactive CD. Strong correlation has been reported between MRE scores and disease activity.\cite{1,11} We also found positive correlation between CDAI and MRE scores as well as between CDAI and MRE + DWI scores. Although the AUC was improved without statistical significance after addition of DWI scores to the MRE scores, stronger correlation was shown between CDAI and MRE + DWI scores. The MRE + DWI scores tended to increase with disease activity. There was also significant difference in MRE + DWI scores between active and inactive CD. These results suggested that DWI with ADC analysis may contribute to MRE evaluation of CD activity.
The mean ADCs of $1.28 \pm 0.47 \times 10^{-3}$ mm$^2$/s in inflamed bowel wall in our study were similar to the $1.2 \times 10^{-3}$ mm$^2$/s reported by Neubauer et al., but lower than the $1.59 \times 10^{-3}$ and $1.98 \times 10^{-3}$ mm$^2$/s in 2 other studies. The differences in ADCs among studies may be related to the different samples and scan parameters including the b values. We used 3 b values of 50, 400, and 800 s/mm$^2$ whereas 2 b values of 0 and 600 s/mm$^2$ were used in the 2 literature reports. The threshold ADC value for differentiating active from inactive CD is not yet established. In 2 studies, which used 2 b values of 0 and 800 s/

**FIGURE 4.** Scatter plot of the mean apparent diffusion coefficients in inflamed bowel segments and Crohn disease activity index shows a moderate negative correlation ($r = -0.71$, $P < 0.001$).

**FIGURE 5.** Receiver-operating characteristic curves of various radiologic findings show higher areas under the receiver-operating characteristic curve of 0.90 for diffusion-weighted MR imaging signal intensities than that of mural thickness (0.83), mural T2 signal intensities (0.80), and contrast enhancement (0.68) for distinguishing active from inactive Crohn disease.
mm² and took magnetic resonance index of activity as reference standard,¹²,¹³ a threshold ADC of $1.6 \times 10^{-3} \text{mm}^2/\text{s}$ had a diagnostic sensitivity of 82.4% and specificity of 100%,¹² whereas an ADC threshold of $1.9 \times 10^{-3} \text{mm}^2/\text{s}$ yielded 96.9% sensitivity and 98.1% specificity in the colorectum, and 85.9% sensitivity and 81.6% specificity in the ileum.¹³ Similarly, using CDAI as reference standard and a threshold ADC of $1.17 \times 10^{-3} \text{mm}^2/\text{s}$, we had 100% sensitivity and 88% specificity.

The DWI hyperintensity was visually greater than that of T2-weighted MRI in the same inflamed bowel wall relative to the adjacent normal bowel wall. As b value increased gradually, the signal intensities of inflamed bowel segments were gradually increased. The interobserver agreement for the scores of DWI signal intensity between 2 radiologists was satisfactory in our study. Diffusion-weighted MR imaging is suitable for the patients in whom oral preparation or intravenous contrast could not be administered.¹ In addition, its rapid acquisition in free-breathing mode with reduction of motion artifacts would be more tolerable in children and weak patients.¹⁰ The intestinal lumen, however, remained hyperintense on high b value DWI because of high viscosity of the bowel content and similar to that of small bowel in another study.¹⁰ We had been careful to avoid the bowel content in the ROI of bowel wall. Second, this study evaluated only 1 intestinal segment in each patient. Actually multiple lesions at different stages of inflammation are frequently observed in CD patients. The assessment only in 1 location with most marked abnormalities might not be sufficient for evaluating the global activity of CD, but we thought it could represent most accurately the CD activity and be applicable to analyze with CDAI. Third, although CDAI is produced more, based on the subjective criteria, it is easy and common to use in clinic. The correlation between the CD activity assessed by endoscopic result and DWI will be analyzed in our next research.

In conclusion, DWI is useful for detecting and localizing active CD. Both DWI and ADC correlated well with disease activity and had excellent accuracy for differentiating active from inactive CD.

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