Research article

Identifying the inflammatory and fibrotic bowel stricture: MRI diffusion-weighted imaging in Crohn's disease

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Abstract

Purpose: To identify inflammatory and fibrotic mural stricture in Crohn's disease (CD) using MR diffusion-weighted imaging (DWI) and to compare DWI findings with those of enteroscope and histological markers.

Method and materials: Thirty-one patients with CD (18 males, 13 females; mean age, 38.9 years) were recruited in this approved retrospective study and an informed consent was obtained from each subject. All subjects underwent bowel MRI examination with conventional and DWI sequences at 3.0 T. Colonoscopy results were distributed within 24 h after examination. According to the endoscopic manifestations and pathological results, the patients were divided into two groups: inflammatory (21/31) and fibrotic (10/31).

Results: In the group of inflammatory stricture, the mean ADC value of stricture bowel was $1.4 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{s}$, whereas $0.8 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s}$ in the group of fibrotic stricture. Inter-group independent sample t-test was performed. A statistically significant difference was observed ($t = 7.403$, $P < 0.05$). The area under receiver-operating characteristic curve was 0.981 (95% confidence interval, 0.943–1.000), with $1.11 \times 10^{-3} \text{ mm}^2/\text{s}$ as the cutoff point. The sensitivity of low ADC values in detecting inflammatory bowels was 90.5%, and the specificity of high ADC values in excluding inflammatory bowels was 100%.

Conclusion: Decreased ADC values in inflammatory stricture bowel may be resulted from multiple factors, including an increase in cellularity, presence of edema, micro-abscesses and increased perfusion. Meanwhile, fibrotic tissue deposition was indicated to lead to restrictions in diffusion. Distinguishable ADCs were observed between inflammatory and fibrotic bowel stricture, where DWI sequence could contribute to the identification.

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Keywords: Crohn's disease; Inflammatory bowel stricture; Fibrotic bowel stricture; Diffusion-weighted imaging; Apparent diffusion coefficient; MRI

1. Introduction

Crohn's disease (CD) is a chronic, relapsing inflammatory disorder of unknown causes with an onset usually in early adulthood. CD is characterized by multiple discontinuous areas of bowel inflammation, distributed throughout the gastrointestinal tract, often complicated by strictures, abscesses, and fistula formations. Stricture is a common complication of CD, occurring in 1/3 of patients after 10 years of disease [1]. Over time, chronic inflammation within the bowel wall progresses to mural fibrosis. When fibrosis is associated with stricture formation, bowel obstruction may develop. It is important to identify fibrotic strictures with certainty because they are unresponsive to medical therapy. Endoscopic examination is a mainstay for evaluation, but is limited in the presence of severe strictures. Medical imaging plays a key role, measuring disease activity, and identifying
complications. It is important to reduce patients’ additional radiation exposure, particularly if they are young or have had multiple scans in a short period of time. Currently, Magnetic resonance imaging (MRI) is regarded to be the optimal imaging modality for assessment of complications of Crohn's disease.

MR diffusion-weighted imaging (DWI) sequence uses the differences in the motion (diffusion) of water molecules in extracellular and intracellular fluid and vascular fluids to produce image contrast, with no need for exogenous contrast materials. This imaging technique provides both qualitative and quantitative information at the cellular level with regards to tissue cellularity and cell membrane integrity and is hence considered a form of functional imaging [2]. Diffusion is inversely related to cellularity, cell membrane integrity and lipopilicity. Restricted (or impeded) diffusion is observed in tissues with high cellularity, e.g., tumors, abscesses, fibrosis and cytotoxic edema [3]. The calculated apparent diffusion coefficient (ADC) is a quantitative measure of tissue diffusivity and is expressed in \((\times 10^{-3})\) as \(\text{mm}^2/\text{s}\). ADCs have been shown to be useful for differentiating severe hepatic fibrosis from mild or moderate fibrosis [4]. Theoretically, DWI should be able to differentiate inflammatory strictures from fibrostenotic lesions in CD due to different water content of the two tissue types. This area is of enormous clinical importance, because the presence of a fibrotic stricture without significant inflammation would direct a patient to surgical therapy rather than continued medical therapy [5]. However, to our knowledge, no study has correlated ADC value of MR DWI sequence — derived estimates of stricture in Crohn's disease with results of matched detailed enteroscope and histological analysis.

The purpose of this study was to identifying the inflammatory and fibrotic mural stricture in CD by using DWI and then to correlate it with endoscopie and histological markers.

2. Materials and methods

2.1. Patient Enrollment

This retrospective study was conducted with approval from the medical ethics committee of the Second Affiliated Hospital of Nanjing Medical University (approved: 2013-KY-034). All enrolled subjects were patients with histologically proven CD. Written informed consent was obtained for performance of the MRI rule and DWI sequence examination, which was the research study. For subjects younger than 18 years, written informed consent was obtained from a parent. Study exclusion criteria included the inability to undergo MRI without conscious sedation, the presence of MRI-incompatible metallic hardware.

2.2. Research play

All MRI examinations were performed by two experienced radiologists independently with the aim of differentiating active inflammatory from fibrotic stricture. Histological findings were used as a reference.

Patients with CD underwent conventional MRI scan and intestinal stricture was located (A stricture was judged present if a bowel segment had \(>80\%\) lumen reduction as compared to an adjacent normal loop and mural thickening of \(>3\,\text{mm}[6]\)). The stricture bowel was divided into six segments: terminal ileum, cecum, ascending colon, transverse colon, descending colon, and rectosigmoid colon. The perianal region and small-bowel loops other than terminal ileum were not specifically assessed in this study. DWI sequence performed in the stricture bowel segment. DWI of the bowel (b values, 0 and 600 s/mm\(^2\)) was independently evaluated by two radiologists (with a combined 10 years of body MRI experience), who were blinded to the clinical and endoscopic examination, on a workstation with commercially available diffusion analysis software (Advantage Windows version 4.6; GE Healthcare). For the ADC measurements, the images were magnified, and the oval regions of interest (ROI) were placed on the largest possible area covering the bowel wall. ROI areas varied from 12 to 30 mm\(^2\). The mean of the two ADC values (measured by different radiologists) was accepted as the ADC value of the segment.

All patients underwent colonoscopy in the next 24 h and had biopsy taken according DWI scanning position (Referring to the bony landmarks such as lumbar, ilium). Histology was adopted as the gold standard. Based on histopathology a stricture was classified as inflammatory or as fibrotic. The ambiguous cases, in which the coexistence of fibrosis and inflammation did not allow an accurate judgment of the actual cause of the stricture, were excluded from the study.

A total of 31 patients (mean age, 38.9 years; range, 21–71 years), including 18 men (mean age, 38.6 years; range, 22–71 years) and 13 women (mean age, 39.3 years; range, 21–63 years), were enrolled in the study.

2.3. MRI technique

All MRI examinations were performed in the supine position with a 3.0 T clinical scanner (Signa HDxt, GE Healthcare) equipped with coil (GE Healthcare) in the abdominal-pelvic configuration (8 radiofrequency channels). No special patient preparation other than a 6-h fast without intake of solid foods was requested prior to MRI. Our protocol required the patient to drink 300 mL of mannitol (2.5%) every 10 min until a total of 1.5 L has been consumed over the course of 60 min just before MRI scanning. Immediately before imaging, all patients were given intravenous administration of 20 mg of scopolamine-N-butyl bromide (Busco-pan; Boehringer Ingelheim, Ingelheim, Germany) to reduce motion artifacts arising from bowel peristalsis.

MRI rule sequences included three-plane localizers, coronal and axial images through the entire abdomen and pelvis: FIESTA (8 mm/10 gap; TR,3.3 ms; TE, 100 ms; matrix, 256 × 128); coronal T2 ssfse through the abdomen and pelvis (single shot fast spin-echo; 5 mm/1 gap; TR/TE, 2800/70; breath-hold); axial T2 fast spin-echo fat-suppressed images through the abdomen and pelvis (4 mm/2 gap; TR/TE, 12000/90; free-breathing with navigator triggering); axial T1 LAVA-Flex Mask through the abdomen and pelvis (4 mm/0 gap; TR/
TE, 4.5/1.7; breath-hold); axial T1 LAVA-Flex through the abdomen and pelvis with three artery phases after injection; and coronal T1 LAVA-Flex through the abdomen and pelvis (4 mm/0 gap; TR/TE, 5.1/1.8; field of view, 40 cm; breath-holds). IV administered contrast agent was gadopentetate dimeglumine (Magnevist, Bayer) at a dose of 0.1 mmol/kg injected at 2 mL/s using a power injector followed by a 20-mL saline flush at the same rate.

MR DWI sequence: axial images; 4 mm/0 gap; TR/TE, 6600/min; matrix, 128 × 128–224; field of view, 40 cm; b value, 600 s/mm²; diffusion of direction, 3 in 1; number of signals acquired, 6.

Total MRI scan times ranged from 45 to 60 min.

2.4. Statistical analysis

Normally distributed data are presented as means ± standard deviation. Paired t tests were used to examine whether there was a difference between the measurements of two radiologists. All data were test with the one-sample Kolmogorov–Smirnov test for normally distributed; groups were compared with the Levene's test for equality of variances. A receiver-operating characteristic curve was constructed for ADC values, and the area under the curve was a measure of the overall ability of discriminating inflammatory and fibrotic stricture bowels. All statistical tests were performed two-sided at the level of P < 0.05. Analysis was performed with the IBM SPSS Statistics 19 software package for Windows.

3. Results

According to the rule MRI manifestations, a single segment of the stricture bowel was chosen to undergo DWI scanning in each patient. A total of 31 DWI sequence data were collected in this study. According to the follow-up colonoscopy, the 31 stricture bowels were divided into group of inflammatory stricture (n = 21) and group of fibrotic stricture (n = 10). MRI manifestations were shown in Fig. 1 and Fig. 2; grouping was summarized in Table 1.

The interobserver agreement in ADC measurements are shown in Fig. 3. The Bland–Altman concordance correlation coefficient was 0.971 (P = 0.000 < 0.05) for the two measurements by two radiologists, and the mean difference was 0.00 ± 0.09 × 10⁻³ mm²/s (P > 0.05). These data suggested that interobserver reliability was very good.

The mean ADC value of proven inflammatory bowels was 1.4 ± 0.23 × 10⁻³ mm²/s (range, 1.01–1.83 × 10⁻³ mm²/s), compared to 0.8 ± 0.16 × 10⁻³ mm²/s (range, 0.534–1.03 × 10⁻³ mm²/s) in fibrotic bowel segments (t = 7.403, P = 0.000 < 0.05) (Table 2). The area under the receiver-operating characteristic curve was 0.981 (95% confidence interval, 0.943–1.000). Using 1.11 × 10⁻³ mm²/s as the cutoff point, the sensitivity of low ADC values for detecting inflammatory bowels was 90.5%, and the specificity of high ADC values for ruling out inflammatory bowels was 100% (Fig. 4).

Fig. 1. A 29-year-old man with known Crohn's disease. Conventional MRI (a–c) shows localized bowel wall thickening, luminal stricture in the descending colon (arrow). The stricture bowel is markedly enhanced (d–e) and accompanied by mesenteric vascular proliferation (arrowheads). Axial diffusion-weighted image (b = 600 s/mm²) through the abdomen (f) shows increased signal and thickening of the descending colon wall. Colonoscopy showed active colitis with ulceration and hyperplastic polyps in the descending colon (h–i).
4. Discussion

In CD patients with strictures, it is important to distinguish between inflammatory stricture and fibrotic stricture, as obstruction in active CD may be relieved by medical treatment whereas fibrotic strictures may require surgical intervention. Rule MRI can provide some information in this setting by differentiating between inflammatory and fibrotic stricture according to the signal intensity of T2WI, the degree and pattern of mural enhancement and changes the mesenteric structure around the lesion segment [6–10]. However, these criteria are lack of quantitative data.

Our results indicate that DWI sequence yields quantitative information (ADC values) and that could contribute to identification of the inflammatory and fibrotic bowel stricture in CD. To our knowledge, this finding has not been previously published.

DWI can provide reliable quantitative measures of lesion bowel, so this imaging tool has been investigated in the assessment of bowel inflammation in CD. There are some studies on the role of DWI in detection of bowel inflammation in CD. ADC may facilitate quantitative analysis of disease activity. Oto et al. [11] reviewed DWI images of 11 CD patients and measured ADC values in a pilot study. They concluded that inflammatory bowel segments showed higher signal and decreased ADC values compared to normal segments. Kiryu et al. [12] found lower ADC values in the disease-active than that in disease-inactive area in CD patients. Neubauer et al. [13] indicated a significant correlation between wall thickness and ADC in inflammatory segments. In conclusion, visual assessment of DWI may provide higher accuracy, and the calculation of the ADC may facilitate the quantitative analysis of disease activity.

It is unclear why intestinal inflammatory lesions have restricted diffusion that is translated into a hyperintense signal on DWI and decreased ADC values relative to normal segments. A potential pathogenetic mechanism may be a reduction in extracellular space secondary to cell swelling or increased cell density. A number of factors may lead to this reduction, including an increase in cellularity, migration of lymphocytes into the inflammatory wall segments, presence of edema, micro-abscesses and increased perfusion. In inflammatory segments, the lamina propria and submucosa are infiltrated by inflammatory cells. Aphtoid ulcers, characteristic lesions of CD, are also strongly associated with lymphoid aggregates. These lymphoid aggregates have restricted diffusion within themselves because of the increased cell density, as well as further limiting the diffusion by narrowing the

<table>
<thead>
<tr>
<th>Position of stricture</th>
<th>The number of stricture bowel (group of inflammatory stricture)</th>
<th>The number of stricture bowel (group of fibrotic stricture)</th>
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<tbody>
<tr>
<td>Terminal ileum</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Cecum</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Descending colon</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rectosigmoid colon</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>10</td>
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limited space in the bowel wall. In addition to the increased number of inflammatory cells, dilated lymphatic channels, hypertrophied neuronal tissue, and the development of granulomas in the bowel wall can further narrow the extracellular space and therefore contribute to the restricted diffusion of water molecules. Accompanying intracellular changes within both the epithelial and inflammatory cells may also have an effect on the changes in diffusion.

In the later stages of CD, mural fibrotic stricture frequently leads to irreversible narrowing intestines associated with proximal bowel obstruction [14]. In CD, fibrosis can involve the entire bowel wall including the mucosa, submucosa, muscularis, mucosa, muscularis propria and serosa layers. Intestinal fibrosis results from an abnormal response to a chronic local injury and is characterized by abnormal production and deposition of excessive extracellular matrix (ECM) proteins by activated myofibroblasts, also called ECM-producing cells [15]. Therefore, collagen fiber deposition in the bowel wall and myofibroblasts have been suggested to play a key role in intestinal fibrosis [9,16,17]. There is also limited information concerning the possible influence of fibrosis on the global DWI signal or ADC values. Several studies have shown that ADCs are lower for cirrhotic liver than normal liver [18] and DWI can be used for assessing the presence of moderate and advanced liver fibrosis [19], possibly because the greater presence of connective tissues in the liver, narrowed sinusoids, and decreased blood flow with cirrhosis [20]. A similar effect of fibrosis may also be possible in the bowel wall. So, fibrotic tissue deposition is known to cause restriction in diffusion.

Wang et al. showed liver parenchyma with chronic hepatitis and without fibrosis had a significantly higher median ADC value than those of parenchyma with each stage of fibrosis [21]. According to Li H et al. [22], there was a decrease in liver ADC with increasing degree of fibrosis, and moderate negative correlations could be found between ADC values and fibrosis stages. In this study it was demonstrated that the mean ADC value of inflammatory bowels was higher than fibrotic bowel segments. We hypothesize that the restriction of fiber deposition on water molecules is greater than the cellular inflammatory edema.

Our study had several limitations due to its retrospective design and small patient population. Firstly, our study population was a small selected group of patients with a high pre-test probability of CD. The analysis was confined to the colon and terminal ileum, where endoscopic correlation was available. The rest of the small bowel was not included in the study. Secondly, although we made our best effort by magnifying images and using oval ROI to try to exclusively cover the bowel wall, we can not completely exclude the possibility of a partial volume effect on ADC measurements. In addition, we selected a b value of 600 s/mm² in this study. Further studies

<table>
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<tr>
<th>Table 2</th>
<th>Statistical comparison between the two groups. Statistics show that all the data of ADC values accord with normal distribution. The data of the two groups meet the homogeneity of variance. There is statistically significant difference between two groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stricture bowel</td>
<td>One-sample Kolmogorov–Smirnov test for normally distributed</td>
</tr>
<tr>
<td>Group of inflammatory stricture</td>
<td>21</td>
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<tr>
<td>Group of fibrotic stricture</td>
<td>10</td>
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investigating DWI findings using different b values may determine their role.

In conclusion, MR DWI sequence enables identification of a stricture segment, definition of characteristics — whether inflammatory or fibrous — and therefore guidance towards the most appropriate treatment. This study shows sufficient promise to merit larger clinical investigations. More cumulative data through prospective large series is necessary to establish their diagnostic role in clinical practice.

References