Magnetic resonance colonography in rats with TNBS-induced colitis: a feasibility and validation study

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Purpose

Magnetic resonance imaging (MRI) is a recently used technique to evaluate colonic inflammation in patients with Crohn disease [1-5]. MR colonography (MRC) provides excellent soft tissue contrast with a short acquisition time and an improved spatial resolution. MRC is able to detect disease activity and evaluate severity in Crohn disease [1-5]. MR changes under treatment are currently under investigation and promising early results have recently been reported [6]. The evaluation of treatment impact on inflammatory lesions also requires the development of innovative treatment evaluation methods at preclinical stage. Many animal experimental models aimed to mimic inflammatory bowel diseases. The 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis model is responsible for lesions close in some regards to those observed in Crohn disease [7]. As colon inflammation is histologically assessed on colon segment after animal death, it does not allow longitudinal follow-up. Very high magnetic field systems are dedicated to small animals. Preliminary results in rodents suggest the feasibility of MRC in colitis models [8-11].

This study aimed to validate the feasibility of MRC in rats with TNBS-induced colitis and compare results with clinical, biological and histological characteristics of the model.

Methods and Materials

Rats and study design

Animal care and experimentation complied with both French and European Community regulations. Sprague-Dawley male rats weighing 200-250g were randomized into a colitic group (13 rats) and a control non-colitic group (6 rats). Colitis was induced at day 0 by administration of TNBS by intrarectal injection through a canula and control rats received the vehicle. The rats were weighed on day of colitis induction and day of MRC. After the imaging session, their colon was removed and weighed to determine the colon weight:length ratio, which is an inflammatory marker and pieces of colon were collected for histological assessment. An inflammatory score ranging from 0 (no inflammation) to 3 (severe inflammation) was determined. Colon concentrations of interleukin (IL)-1# and TNF# were measured. Colon expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) was determined by Western blot.

MRC

MRC was performed 2 days after colitis induction (Bruker 4.7 T BioSpec 47/40 USR). The rats were anesthetized with an intraperitoneal injection of thiopental. They were transferred onto a cradle in the prone position during procedure. We used a T2w
RARE (Rapid Acquisition with Relaxation Enhancement) sequence with and without fat suppression; TR 4630 ms; TE 30 ms, Matrix 320, Slice 1 mm, NEX 3, Flip Angle 180°, FOV 6 cm; imaging time: 7 minutes and a T1w FLASH (Fast Low Angle Shot) sequence; TR 215 ms; TE 3.6 ms, Matrix 256, Slice 1 mm, NEX 1, Flip Angle 80°, FOV 6 cm; imaging time: 14 minutes.

MR images were analyzed with ParaVision 5.0 software. They were submitted to blind interpretation by the same radiologist. The quality of the examination was assessed by wall and motion artifacts rated each 0 to 3. All measurements were performed in the descending part of the colon as it keeps a longitudinal axis therefore allowing the study of accurate transversal slices. Criteria for colon inflammation assessment were: - colon wall thickness (minimal, maximal and at kidney hilum level), - colon wall signal intensity in ROIs on T2w images, - presence or not of a target sign pattern, - presence or not of irregular patterns of mucosal colon wall surface corresponding to ulcerations, - presence or not of a spontaneous T1w hypersignal intensity in the colon wall.

**Results**

**MRI data**

The quality was excellent in 12 exams, good in 4 exams and poor in 5 exams. Colon wall thickness at day 2 was significantly higher in the TNBS group than in the control group: maximal thickness (0.95 ± 0.16 vs. 1.57 ± 0.17mm), thickness at kidney hilum level (0.45 ± 0.04 vs. 0.92 ± 0.09mm) and minimal thickness (0.42 ± 0.03 vs. 0.72 ± 0.07mm) (respectively p=0.04, p=0.004 and p=0.017; **Figure 1**). There was a trend for increase in wall signal intensity on T2w images at day 2 in TNBS rats (116.7 ± 10.7 vs. 81.9 ± 16.3; p=0.09; **Figure 2**). The appearance of a target sign pattern was observed in 7 out of 13 TNBS rats and in none of the 6 controls on day 2 MRI examination (p=0.02) (**Figure 3**). Irregular patterns of mucosal wall surface were found in 8 out of 13 TNBS rats and in none of the 6 controls on day 2 MRI session (p=0.01), and spontaneous T1w hypersignal intensity was observed in the colon wall in 9 out of 13 TNBS rats and in 1 out of 6 controls on day 2 MRI examination (p=0.03) (**Figure 4**).

**Comparison of MRI data to inflammation parameters**

Minimal thickness was correlated with colon weight:length ratio ($r^2=0.56$, p=0.002) and to a lesser extent with inflammatory markers. Minimal thickness was also significantly higher with an inflammatory score of 2 or 3 (moderate or severe) compared to a score of 0 or 1 (absent or mild) (p=0.04). Thickness at kidney hilum level was correlated with colon weight:length ratio ($r^2=0.45$, p=0.009) and IL-1# production, with a strong trend for other inflammatory markers. Signal intensity on T2w images was strongly correlated with colon weight:length ratio (Pearson $r=0.8131$, p=0.0004 and Spearman
r=0.8198, p=0.0003) and IL-1# production, and to a lesser extent with iNOS and COX-2 expression. It was significantly increased when inflammation was histologically observed (score greater than or equal to 1) (p=0.03). Colon weight:length ratio differed significantly in the presence of the appearance of a target sign pattern (p=0.0002). All biological inflammatory parameters except iNOS expression differed significantly in the presence of the appearance of a target sign pattern. Colon weight:length ratio also differed significantly in the presence of an irregular pattern of mucosal wall surface (p=0.02), as well as inflammatory markers excepting iNOS. Colon weight:length ratio (p=0.009) and IL-1# production differed in the presence of spontaneous T1w hypersignal intensity.

Images for this section:

**Fig. 1:** MRC of rats, coronal T2w abdominal images: 1a. control rat - colon wall is thin, regular with a moderate signal (arrow) / 1b. colitic rat - colon wall is thickened, irregular with increased signal (arrow)
Fig. 2: MRC of rats, axial T2w abdominal images: 2a. control rat - colon wall is thin, with a moderate signal (arrow) / 2b. colitic rat - colon wall is thickened, with increased signal (arrow)
**Fig. 3:** MRC with axial T2w abdominal image of a colitic rat - colon wall is thickened and shows a target sign (arrows)
Fig. 4: MRC of rats with TNBS-induced colitis at day 2, axial T1w abdominal images: 4a. colon wall shows spontaneous hypersignal intensity (arrow) / 4b. colon wall shows irregular mucosa (arrow)
Conclusion

Our study shows that MRC is a reliable technique and of satisfying quality in rats with TNBS-induced colitis. In our experimental conditions, 2 days after colitis induction, MRC succeeded in properly distinguishing colitic rats from controls in the acute inflammatory phase. In addition to common criteria such as wall thickness, T2w signal or visible ulcerations with an irregular pattern of mucosal surface, we described 2 original criteria in animal models using MRI: the appearance of a target sign pattern and intramural hemorrhage detection. The criteria most associated with clinical and biological inflammatory markers are minimal wall thickness, signal intensity on T2w images and the appearance of a target sign pattern. Our work validates high field MRC as a useful tool in the assessment of acute inflammation of the colon, so that it may be used in the early phase of forthcoming longitudinal therapeutic protocols.

References


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