MRI derived small bowel motility as a marker of Crohn's disease activity

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Introduction

Rational use of immunosuppressive therapies in Crohn's disease relies on accurate identification of those patients with acute inflammation ('active disease') who are most likely to respond to medical treatment. Magnetic Resonance Enterography (MRE) is playing an increasingly important role in the disease grading process complementing established symptomatological, biochemical and histopathological markers. A number of anatomical features seen on MRE have been shown to correlate closely with disease activity including mural thickening, T2 signal, mural enhancement and perimural oedema[1,2]. Abnormal intestinal motility is also well described in Crohn's disease and preliminary data based on subjective assessment of "cine capture" MRI suggests it may also be a marker for disease activity[3]. However quantitation of intestinal motility remains mostly unexplored owing to its functional complexity[3-5]. Using an advanced, non-rigid registration technique, objective quantitation of bowel wall motion can be performed. We explored the relationship between Crohn's disease activity and intestinal motility. Quantification of small bowel motility as a biomarker of inflammation was validated against two standards of reference 1) histopathological grading of bowel wall inflammation and 2) preexisting validated anatomical MRE markers of inflammation. In addition we investigated whether quantification of motility could be used to improve the predictive abilities of MR for acute inflammation in addition to existing anatomical markers.

Methods

Patients: Review of the departmental database revealed 23 patients (mean age 35 range 16-71, 15 female) fulfilling the eligibly criteria of previous histological diagnosis of Crohn's disease and undergoing both MRE and full ileocolonoscopy within 30 days of each other (mean 5 days). 12 had been diagnosed with Crohn's in the previous five years and the majority (n=17) had not undergone previous surgery.

MRI Protocol: All MR scans were performed using a 1.5T Siemens Avanto scanner (Siemens, Erlangen, Germany). Patients fasted for 4h and then ingested 1.5L of Locust bean gum and 2% mannitol solution before adopting the prone position in the scanner. For motility analysis, sequential coronal TRUEFISP (20 second breath hold, TR=(3.77-3.98ms), TE=(1.89-1.99ms), slice thickness 10mm, 1 slice/0.8sec) sequences were acquired through the abdomen to include the small bowel volume (range 8 to 16 acquisitions per patient). An anti-spasmodic was then administered (20mg Buscopan, Boehringer Ingelheim, Ingelheim) and standard anatomical sequences were performed (axial/coronal TrueFISP, axial/coronal HASTE and coronal VIBE)

Quantitation of small bowel Motility: (i) Registration: An optic-flow based registration technique was extended to incorporate image intensity changes[8]. The 2D slices of a time series were registered to a representative slice to generate deformation fields and maps of intensity change.

(ii) Region of Interest (ROI) placement: A single observer (consultant radiologist 7 year's experience of MRE), blinded to all clinical data, drew a region of interest (ROI) within the last 3cm of the terminal ileum on the representative slice. Using the deformation fields from the registration, the ROI was automatically propagated to all slices of the time series with no manual intervention. The area of the ROI over the slices is shown in Figure 1a. To evaluate a motility index, the standard deviation of the Jacobian determinant (a measure of local area change) was used to quantify the motion of pixels within the ROIs.

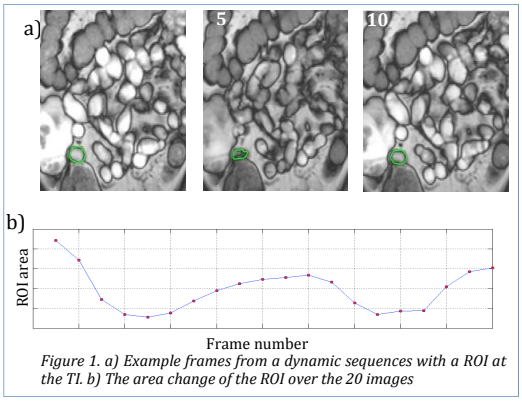

Figure 1. a) Example frames from a dynamic sequences with a ROI at the TI. b) The area change of the ROI over the 20 images

Reference standard for acute inflammation (i) Histopathological grading of disease: In each patient at least 1 (mean 3) terminal ileal biopsies were taken at ileocolonscopy. Following hematoxylin-eosin staining, biopsies were reviewed in consensus by two experienced histopathologists (3 and 10 years' experience) who applied an endoscopic biopsy Acute Inflammation Score (eAIS) based on typical morphological features of Crohn's disease providing a histopathological activity reference[6]. The biopsy showing the highest score was used for subsequent analysis **(ii) Anatomical grading of disease activity:** Two consultant radiologists (4 and 6 years of experience) applied a previously validated MRE score of disease activity based on anatomical MRI features described by Steward et al[7]. Specifically both observers reviewed all 23 datasets using a PACS viewing system, unaware of the motility sequences or clinical information and in consensus graded activity in the last 3cm of the TI via qualitative scoring (0-3) of mural thickness, mural T2 signal, mural enhancement and perimural oedema. The sum of the scores of these 4 parameters for each patient constituted the anatomical MR activity index[7].

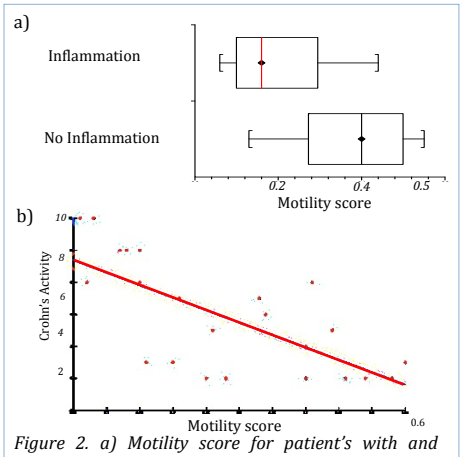

Figure 2. a) Motility score for patient's with and without evidence of inflammation on biopsy. b) Motility score against activity grading based on anatomical MR index

Statistics: Shapiro-Wilk test ($\alpha = 0.5$) was used to examine normality of MRE data and histopathological grading. Kendall's Tau correlation was used to examine the relationship between 1) The Motility Index and histopathological grading and 2) The Motility Index and anatomical MRI activity grading. An un-paired T-test was used to investigate the relationship between the patients with and without evidence of activity assessed by histopathology against motility. Finally, the ability of the motility index to predict histopathological inflammation over and above the basic anatomical MRI grading was tested by building a linear regression model.

Results

Motility score and histopathological correlation: Across the 23 patients, the mean motility index was 0.28 range (0.06-0.55) and the mean histopathology score (eAIS) was 2 (range 0-5). The Motility index of the non-inflamed terminal ileum (eAIS score = 0) was significantly greater than bowel exhibiting active disease (eAIS >0) p=0.0027 (tstat -3.3, df27) (figure 2a). Correlation with Kendall's Tau demonstrated a significant negative correlation between the motility index and histopathological grade of inflammation (R = -0.37, p = 0.028).

Anatomical MRI grade against histopathological reference: Mean anatomical MRI grade (sum of T2 signal, Mural thickness, Mural enhancement and peri-mural oedema scores) was 4 (range 0 to 10). There was a statistically significant negative correlation between anatomical MRI grade and histopathology (eAIS) score (R = 0.54, p = 0.002)

Motility score and Anatomical MRI grade: There was a statistically significant, negative correlation between the anatomical MRI grade and motility index (R = -0.56, p = <0.001) (figure 2b).

Regression analysis: The regression model confirmed anatomical grading was a statistically significant predictor of histopathological eAIS score (regression coefficient 0.25 (95% CI 0.02 to 0.48), p=0.04. However addition of motility index to the model did not produce any statistically significant advantage (regression coefficient -0.1 (95% CI -0.62-0.41), p=0.68

Discussion

A significant correlation has been demonstrated between software quantified small bowel motility and existing standards of Crohn's disease activity in the form of 1) histopathology and 2) established and validated anatomical MRE markers of activity. Collectively these data suggest motility is a useful biomarker acute inflammation in Crohn's disease activity. However whether motility adds to the ability of anatomical grading of MRE features to predict activity remains open to question.

References 1. Taylor *et al.* 2009 Radiology, 2. Horsthuis *et al.* 2009 EJR, 3. Froehlich *et al.* 2010 EJR, 4. Patak et al. 2011 ESGAR, 5. Menys *et al.* 2011 ESGAR. 6. Stange *et al.* 2006 Gut. 7. Steward *et al.* 2011 EJR, 8. Odille *et al*. 2011 MRM