Quantitative assessment of terminal ileum motility on MR Enterography in Crohn's disease: a feasibility study in children

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Abstract:

Purpose: To investigate the relationship between software quantified terminal ileal (TI) motility and histopathological activity grading, a standardised MRI activity score Crohns Disease MRI Index (CDMI) and faecal calprotectin.

Methods: A review of a tertiary referral paediatric hospital imaging database was performed to identify subjects with Crohns disease or unclassified inflammatory bowel disease (IBDU) who underwent dynamic MRI Enterography (MRE) bowel motility assessment. Dynamic imaging for 25 patients (median age 12, range 5 to 16) was analysed, blind to any clinical data, with a previously validated motility assessment algorithm (GIQuant®, Motilent, London, UK). A region of interest was placed in the terminal ileum (TI) within 3cm of the ileocecal valve and the motility score derived. The primary SoR was TI histopathological Endoscopic biopsy Assessment of Inflammatory Activity (eAIS) occurring within 40 days of the MRI. Our secondary SoRs were: 1) the Crohns Disease MRI Index (CDMI), a standardised MRI activity score validated against eAIS and 2) faecal calprotectin (FC) levels within 3 months of MRE.

Results: MR Enterography derived median motility score was 0.17 (interquartile range, IQR 0.12 to 0.25) and median CDMI was 3 (IQR 0 to 5.5). Based on the primary SoR, 43% of patients had active disease (eAIS>0) with the median eAIS score of 0 (IQR 0 to 2; range 0 to 5). Correlation between eAIS and motility was $r = -0.58$ ($p = 0.004$, $N = 23$) and between CDMI and motility was $r = -0.42$ ($p = 0.037$, $N = 25$). Motility score was lower in those with active disease (median 0.12 vs 0.21, $p = 0.020$) while CDMI was higher (median 5 vs 1, $p = 0.04$). In a subset of 12 patients with faecal calprotectin within 3 months of MRE, correlation between and motility was $r = -0.27$ ($p = 0.4$).

Conclusion: Quantified terminal ileal motility is significantly negatively correlated with histopathological activity, reproducing findings in adult populations. TI motility also shows a

significant negative correlation with a structured MRI activity score but did not show a significant correlation with faecal calprotectin.

Introduction:

Quantitative assessment of terminal ileal motility is inversely correlated with disease activity in adult Crohns disease[1–3]. Bowel wall motility therefore has the potential to act as a reproducible treatment biomarker as part of the standard MR enterography protocols [4]. Extrapolation to paediatric patients however cannot be assumed. Paediatric onset inflammatory bowel disease (PIBD) may be a different entity or at least exhibit differences in terms of natural history and aetiology compared to adult-onset IBD. Children are more likely to present with pan-enteric disease and the inflammatory sub-type is more common than the fibrostenosing or penetrating subtypes[5, 6]. Early and very-early onset IBD (defined as disease presenting before 10 years and 6 years respectively) are associated with single gene mutations in specific pathways including IL-10 and XIAP [7]. This is very different to the multi-factorial causality seen in adult-onset disease.

In addition, MRE acquisition protocols often differ from those used in adult cohorts. Whilst some institutions now routinely include cine MRI sequences in paediatric protocols, the breath-hold techniques used in adults can be very challenging in children [8], and a free-breathing acquisition is often preferred. This can affect image quality and has implications for the accuracy of image quantification software. Overall therefore caution is needed before assuming the utility of quantified small bowel motility in paediatric cohorts without supportive evidence. To our knowledge, no study has yet investigated the utility of quantitative assessment of small bowel motility in paediatric Crohns disease patients.

The purpose of the study was to investigate the relationship between software quantified terminal ileal (TI) motility, histopathological activity grading, the standardised MRI activity score: Crohns Disease MRI Index (CDMI) and faecal calprotectin (FC) levels.

Methods:

Participants

Ethical approval was granted by our local scientific committee and the Royal Free Medical Ethics committee (REC number 10/H0720/91GOSH, R&D Ref 18BB10) for this retrospective study.

A search of the departmental Picture Archiving and Communication System (PACS) and the local gastroenterology database was performed to find all paediatric patients with a confirmed diagnosis of paediatric inflammatory bowel disease (PIBD) who had undergone MRI enterography (MRE) and Endoscopy within a one year of each other between 2012 and 2018. 204 patients were identified (88 female). Studies were excluded if; the patient did not have a diagnosis of Crohns or Crohns-like unclassified IBD (IBDU) (n=59), the child had undergone prior resection of the terminal ileum (n=7), cine sequences were not performed, the scans were too degraded by artefact or abandoned (n=7) (as assessed by a paediatric radiologist; 8 years' experience in paediatric MRI).

A heterogeneous group of 131 subjects (53 female) were identified with a mean age of 11.5 years (range 5 to 18). These children were a typical cohort of patients under the care of a tertiary paediatric IBD centre and included new diagnosis and follow-up cases. The full gamut of medical treatment regimens including anti-TNF alpha-blockers was represented in the cohort. A subset of these patients, who had undergone endoscopy with terminal ileum biopsy within 40 days of MRE was selected for the primary analysis (see below). For the secondary analysis using a standardised MRI scoring system, we chose to include 2 patients with TI histology whose endoscopy fell outside of the 40 day limit (55 and 83 days respectively between studies) to increase our sample size. We justify this on the basis that the MRI scoring system and TI motility are both derived from the same MRI study and a reference standard is not necessary to assess simple correlation between the variables.

A study flow chart is shown in Figure 1.

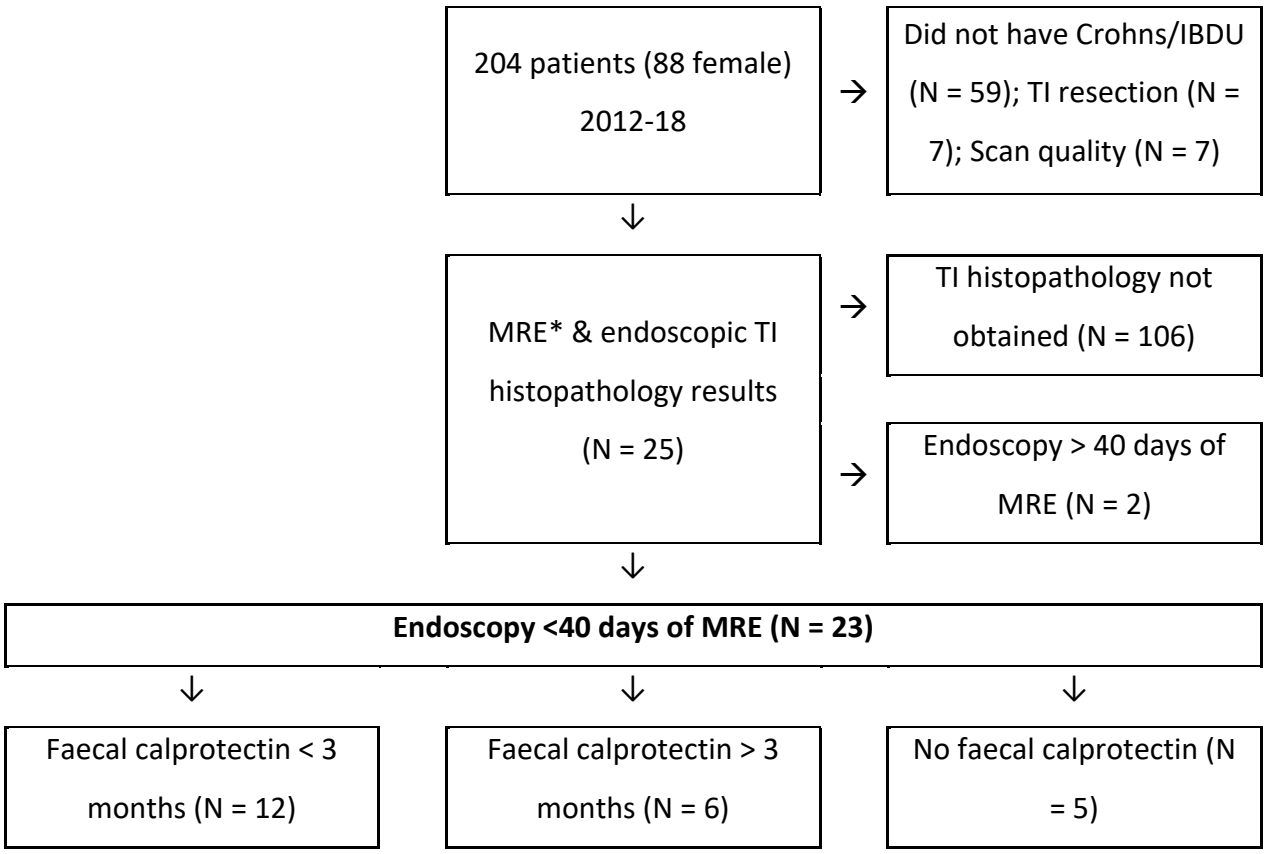

*Figure 1 Identification and selection of patients included in the analysis. * a sample size of 25 was used to compare the Crohns Disease MRI Index (CDMI) and TI motility*

MR Protocol

All subjects were scanned according to the institution protocol which includes a 4h fast before the consumption of up to 1500mL hypo-osmotic oral contrast agent (3% Mannitol solution). Patients were cannulated and positioned supine on the MR bed. The manufacturers body coil was used. Each scan lasted approximately 45 – 60 minutes including motility, T2, diffusion-weighted, and contrast enhanced sequences (institutional protocol has been published previously [9]).

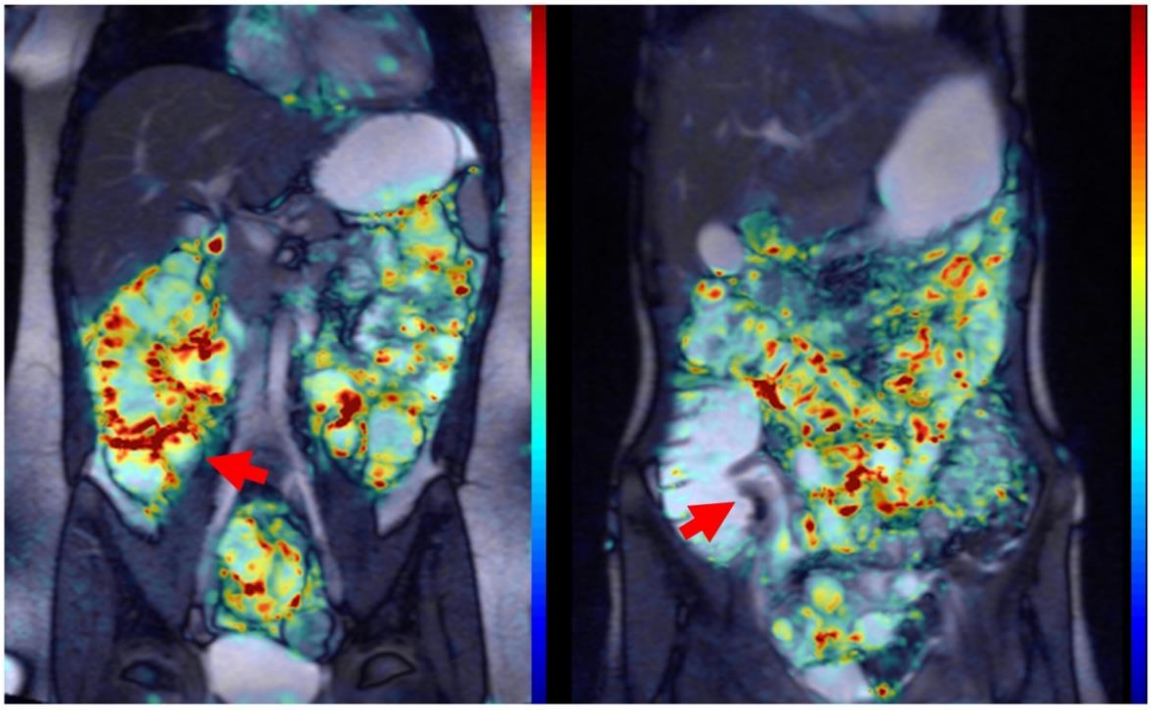

Figure 2 Anatomical reference image overlaid with motility map (red = high motility, blue = low) showing the terminal ileum (left, red arrow) of a patient with a low symptom score and high motility compared to the terminal ileum (right, red arrow) of a patient with a high symptom score and low motility

Two different MRI scanners were used over the 6y period from which the study data was collected, a 1.5T Siemens Avanto and a 3T Siemens Prisma. A summary of the two sequences is provided in Table 1. The cine imaging involved a whole abdomen balanced steady-state free precession coronal acquisition which takes approximately 30 second to acquire. This is performed in free breathing and multiple acquisitions are repeated over a 5-minute interval. The datasets are reconstructed according to slice location and then sent to PACS to be viewed and analysed as a cine loop.

Image analysis

Data was de-identified before being processed using GIQuant® (Motilent, London UK). GIQuant is a CE marked motility analysis tool producing a quantitative motility map and anatomical reference image with the methodology described previously [1, 10]. For each dynamic series at a single slice position, one map and one reference image were generated.

Each voxel in the map represents the amount of deformation at that voxel location through time. The more movement of the bowel (e.g. through peristalsis) the higher the motility score.

The motility score was generated through region of interest analysis (ROI) in Horos (V2.0.0 RC3). Because all datasets were acquired with free breathing techniques, it was necessary to correct for this respiratory artefact using a technique called: Dual Registration of Abdominal Motion (DRAM) [11]. A paediatric radiologist (8 years' experience with paediatric small bowel MRI) identified the location of the terminal ileum and placed a ROI over the final 3 cm, including the ileo-caecal valve blind to the motility map or cine series. The ROI was transferred through copy and paste function to the motility map by a clinical scientist with (10 years' experience in small bowel motility MRI) and the mean motility score recorded for each subject TI.

Crohns Disease Activity Assessment

Primary standard of reference

Histopathology - Endoscopic Acute Inflammatory Score (eAIS): The eAIS score includes measures of epithelial damage, architectural changes in the mucosa, epithelial neutrophils, erosion and/or ulceration, and the presence of granulomas. It is based on typical features described by the European Society of Crohns and Colitis in their consensus paper on Crohns management in 2006 and proposed by Steward et al [12, 13]. Scores were calculated using the original biopsy samples taken at the terminal ileum. In summary, each biopsy specimen was reviewed in face-to-face consensus by two experienced paediatric pathologists (with 18 years and 25 years of experience, respectively) who were blinded to clinical information other than the diagnosis of Crohn disease. Patients with an eAIS = 0 are considered to be in remission.

Secondary standards of reference

Crohns Disease MRI Index (CDMI): The CDMI score for the terminal ileum was calculated by a paediatric radiologist (8 years' experience in paediatric small bowel imaging). This score was originally validated by Steward et al [13] for use with the eAIS histopathology reference standard and given eAIS is our histopathological gold standard we preferred this method over other activity scores [13]. It is a semi-quantitative MRI activity score with 4 variables; wall thickness, T2 wall signal, perimural signal, and extent of enhancement. According to Steward et al, a simple sum of the variables is the preferred method for correlation.

Faecal Calprotectin

Faecal calprotectin (FC) is considered to be a reasonable marker of overall inflammatory burden within the GI tract. The FC levels in stool have been shown to correlate with the serum CRP and other faecal markers of inflammation such as faecal lactoferrin FC levels also predict endoscopy findings[14].

Statistical analysis:

Data was analysed using R Version 3.1.0 (Vienna, Austria). Data was checked for normality and correlation was performed between motility against eAIS, CDMI and FC levels. Where significant relationships were found the data was dichotomised based on the disease severity indices cut-off for remission and the difference between groups (remission and active disease) calculated and checked for significance using t-test [15]. The Area Under the receiver operating characteristic Curve (AUC) for quantified TI motility was constructed using dichotomised data, divided into active disease (eAIS >0) and remission (eAIS =0). Statistical analysis was performed in RStudio (Version 1.2.1335, Vienna, Austria) and receiver operating characteristic analysis was performed with the pROC package using the with the non-parametric DeLong method [16][17].

Results

Histopathological assessment

A subset of 23 patients (median age 12, range 5-16, 13 female) with MRE and terminal ileal biopsy within 40 days was identified for primary analysis (Figure 1; Table 2). The median eAIS score, rounded to the nearest integer, was 0 (range 0 to 5) and median motility score was 0.17 (interquartile range, IQR 0.12 to 0.25). There was a moderate negative correlation between eAIS and motility r = -0.58 (p = 0.004) (Figure *3*, left).

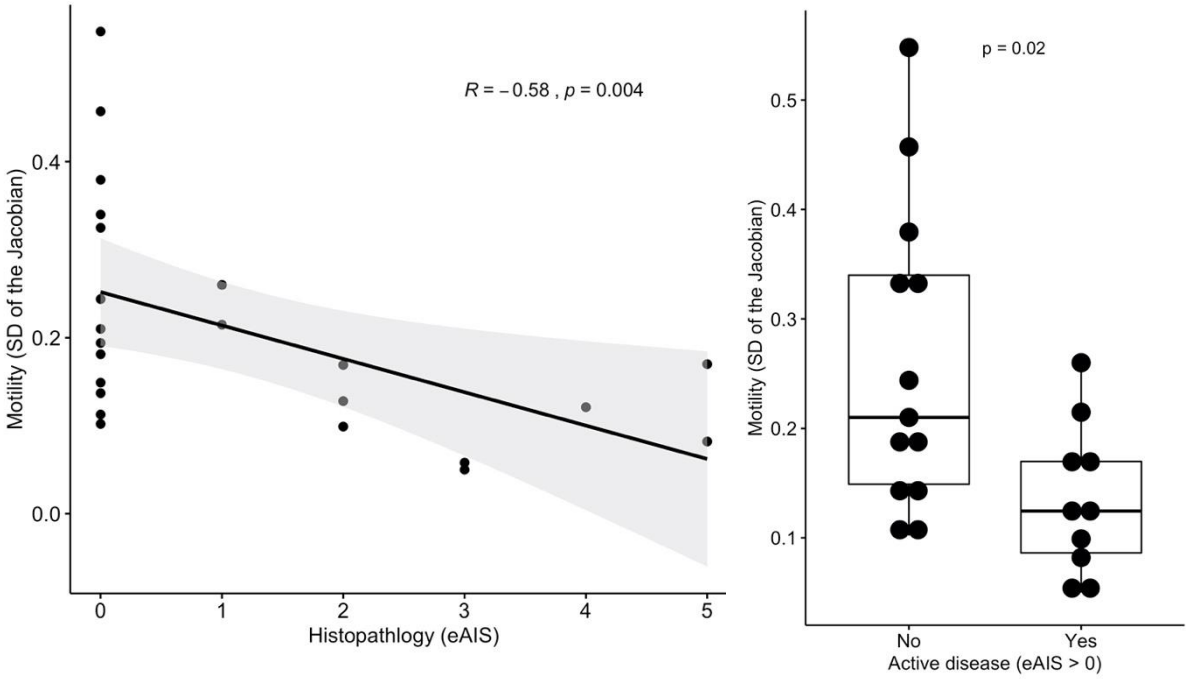

Figure 3 Relationship between endoscopic biopsy assessment of inflammatory activity (eAIS) and terminal ileal motility quantified as the standard deviation (SD) of the Jacobian determinant derived from 'cine' MRE images. TI motility is negatively correlated with eAIS (left) and significantly decreased in patients with active disease

The cohort was dichotomised into active disease (eAIS >0) and remission (eAIS =0). The median motility in the active group was 0.12 (IQR 0.09 – 0.17) and in remission was 0.21 (IQR 0.15-0.34). The difference between groups was 0.09 (p = 0.02) (Figure *3*, right).

A further assessment of the dichotomised data, into active disease (eAIS >0) and remission (eAIS =0), was assessed by calculating the Area Under the receiver operating characteristic Curve (AUC) of 79.2% (deLonge 95% CI: 60.5% to 98.0%).

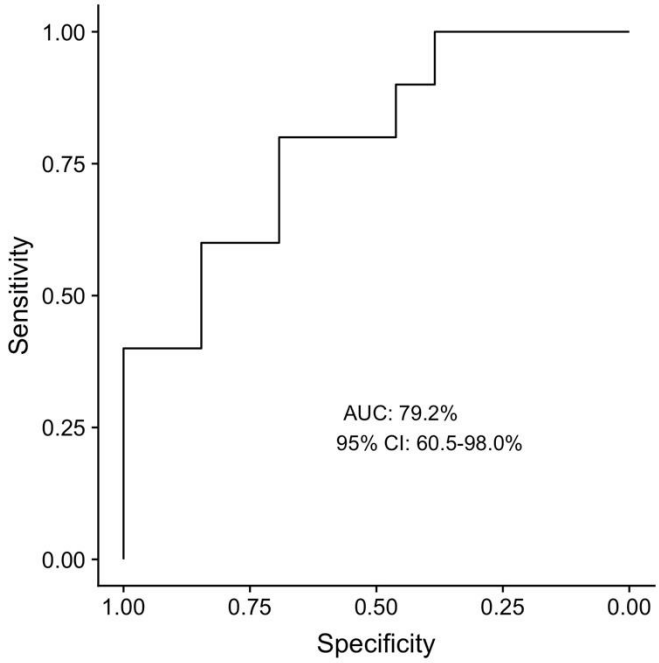

Figure 4 Quantified TI motility Area Under the receiver operating characteristic Curve (AUC) for endoscopically confirmed active disease (eAIS >0)

Secondary standards of reference

Crohns Disease Activity Index (CDMI)

A subset of 25 patients (Mean age 12.2, range 5-16, 14 female) was derived for analysis. This includes the 23 patients from the primary endpoint analysis and 2 additional patients with available TI histology but where endoscopy was performed outside of the 40 day cut off. Correlation between TI CDMI and motility was r = -0.42 (p = 0.037) and CDMI was higher in patients with active disease (eAIS > 1) compared to those in remission (median 5 vs 1, p = 0.019).

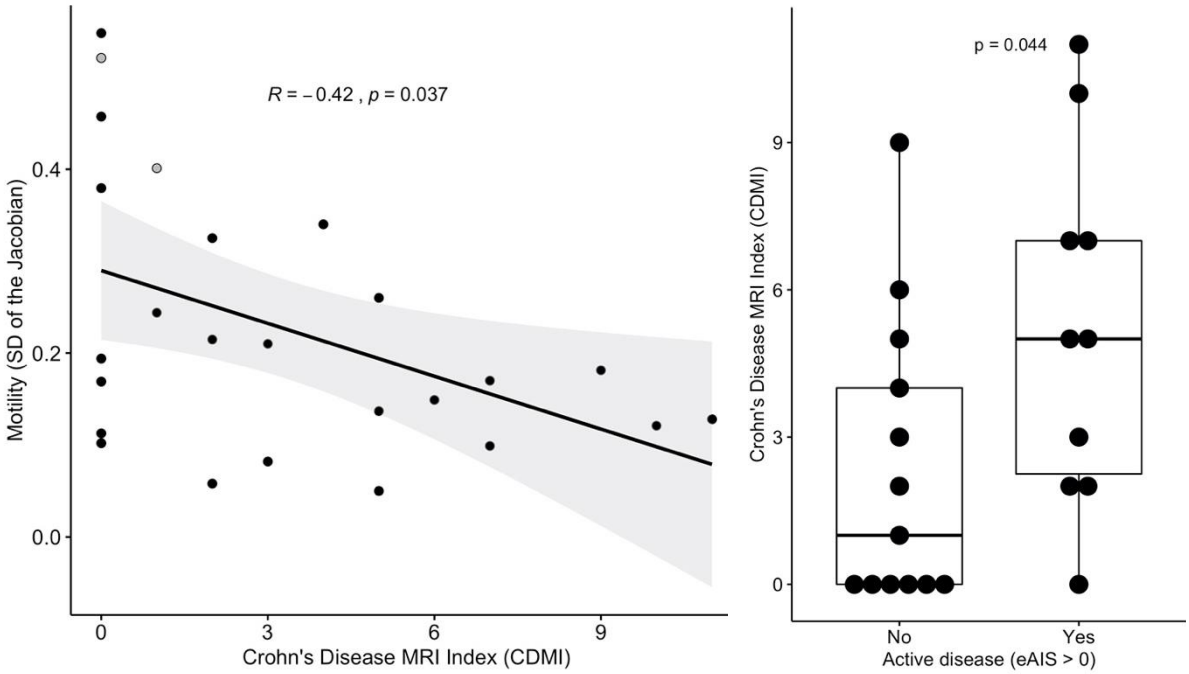

Figure 5 Relationship between Crohns Disesase Activity Index (CDMI) and terminal ileal motility quantified as the standard deviation (SD) of the Jacobian determinant derived from 'cine' MRE images. Black: MRE & endoscopy within 40 days; Grey: MRI & endoscopy >40 days apart.

Faecal Calprotectin

In a subset of 12 patients (mean age 11, range 7-15, 9 female) with FC levels within 3 months of MRE, correlation between faecal calprotectin and motility was r = -0.27 (p = 0.4).

Discussion

In this study we present an initial experience of quantified small bowel motility analysis using MRI, to assess CD activity against a histopathological standard, an MRI activity standardised score, and a global assessment of inflammatory burden (FC). A negative association was seen between terminal ileum motility and all measures of disease activity, and this was significant against the primary histopathological endpoint and against the MRI activity score. These findings reproduce observations in adult populations [2, 3, 18, 19] and this work provisionally supports the use of quantified MRI motility as a candidate biomarker for disease activity in paediatric patients.

Children are often unable to hold their breath and have a greater variation in body size and tolerance to the scanning environment. At the outset, we questioned whether quantified motility software would produce results with cine sequences acquired in free breathing. The motility assessment software has built in respiratory motion correction and there did not appear to be any overt bias in the data. The number of time points (i.e. the temporal resolution) within the cine data was at the lower end of acceptability. However, the summary measure takes the standard deviation of the deformation caused by small bowel motion and is generally robust to around 10 time points over 10 seconds [10]. Our data indicates that we can derive motility data from free breathing cine sequences and therefore this technology can be potentially used in paediatric MRE.

The negative correlation between motility and histopathology (eAIS) at the terminal ileum reproduces previous findings from both retrospective and prospective studies in adults [1, 10, 20]. It is likely that as the bowel wall becomes inflamed its ability to peristalse becomes reduced. Indeed, this process appears reversible in adults where treatment is effective [4], though we did not formally assess this and our study includes both new and follow-up patients. In this study, we limited our radiological and histological assessment to the final 3cm of the ileocaecal valve region as the most robust way of establishing anatomical correspondence between imaging and histopathology. Even with small numbers, a significant association was found.

Crohns disease MRI activity scores are well-validated for use in the assessment of disease activity [21] and it is reassuring that the CDMI score in the TI showed a negative correlation with quantified TI motility. We allowed 2 cases where endoscopy occurred >40 days from the MRE. We justify this on the basis that the CDMI and motility are derived from the same MRI and the scores are not influenced by the endoscopy and do not require a reference standard to derive simple correlation. In adult studies, motility has been shown to correlate with MRI activity scores such as MEGS [22] which includes more variables than the CDMI score, such as DWI. However, we chose the CDMI score in this paper because it is validated against our primary standard of reference eAIS [13]. We also chose to score the terminal ileum only, rather than the whole small bowel as per the other endpoints in our study.

An interesting finding in our data was the wide range of motility scores when eAIS = 0 (range 0.1 – 0.55). Two adults studies [23][19] have shown that small bowel unaffected by inflammation may still demonstrate reduced motility in patients with Crohns disease. Menys et al postulate that this may explain why 20% of patients with complete mucosal healing, demonstrate no improvement in symptom burden [19]. The wide variation in our data could be a result of this phenomenon. The fact that faecal calprotectin levels did not correlate with motility may also support this theory. If unaffected/healed small bowel can be dysmotile then even in the presence of a normal or reducing FC level, the patient may be symptomatic. We did not formally assess this in our population but this would be an interesting focus for future studies. Given the findings by Menys et al, it would be interesting to prospectively compare motility and patient-reported symptoms in patients defined as 'in remission' according to mucosal end-points.

Our study does have limitations. Chief amongst these is the small and heterogeneous sample. At our institution, endoscopy and MRI often do not occur in close proximity due to the need for a general anaesthetic as part of the endoscopy procedure which restricts flexibility in the scheduling of the two studies. In order to draw valid inferences from the data, it was necessary to keep the time between endoscopy and MRI as short as practical. We chose 40 days because this allowed us to keep a relatively large study group whilst limiting the effect of any interval therapeutic intervention change. Increasing the permissible gap to, for

example, three months, would allow greater study numbers but risk increased confounding factors over such a wide time window. The next step is to repeat this study as a prospective trial limiting the time difference between biopsy and MRI as far as possible. Ideally studies performed within one week of each other would be optimal, though this may be logistically difficult.

For faecal calprotectin levels we had to widen our study window to three months either side of the MRI to include sufficient data for our histopathology group and this is likely to further confound assessment of this reference standard, which did not reach significance with motility. In addition, it is perhaps not surprising that a global assessment of inflammation does not correlate with focussed analysis of a single section of bowel.

Our patient group was composed of new and established patients so study participants would have been exposed to range of different therapies. Although this is likely to have influenced our results significantly, the purpose of this study was to demonstrate that motility software could be used in children using free breathing techniques and could produce results similar to those seen in adult trials. The group is representative of a typical tertiary paediatric IBD referral centre. Future work would need to account for variations in patient management.

Another limitation of this study is the retrospective data collection. An improvement would be expected in the quality of data and potentially in the results between a retrospective and prospective investigation. Although the MRI data is straightforward to use from a historical perspective, the collection of patient symptoms from clinical notes and endoscopy reports/images does introduce subjectivity into the study. We attempted to control for this by blinding the clinical observers to the MRI data ahead of their scoring. We also blinded the radiological reviewer to the motility data with all ROI calculations being made on a single coronal dataset without motility information. In general, this helped to limit bias but, again prospective assessment would strengthen this aspect of this investigation.

Despite limitations, there are a number of benefits to pursuing this work. First, motility assessment provides an objective score based on a physiological process that can be tracked through time. In adults, recent research shows that tracking motility through time can predict

response to treatment [4]. The motility score can be obtained without the need for a spasmolytic agent or intravenous contrast with the latter being under scrutiny due to concerns regarding the potential effect of gadolinium accumulation in the brain [24]. Both require intravenous access which can be challenging in children. The motility score is quick to perform, taking <60s for the radiologist to identify the ROI and for the software to produce a reportable score for clinical interpretation. This is considerably less than the time necessary to produce a standardised MRI activity score such as CDMI, which can take several minutes depending on case complexity and reporter experience. In combination with a standardised report, motility may facilitate a fast and reproducible tool for disease quantification.

In conclusion, quantitative assessment of terminal ileal motility is feasible in children using standard free-breathing techniques. Based on a small cohort of patients with Crohns disease, there is a negative correlation between TI motility and disease activity, reproducing the findings in larger adult studies.

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