Magnetic Resonance Enterography Cannot Replace Upper Endoscopy in Pediatric Crohn Disease: An Imagekids Sub-study

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ABSTRACT

Objectives: Although magnetic resonance enterography (MRE) can accurately reflect ileal inflammation in pediatric Crohn disease (CD), there are no pediatric data on the accuracy of MRE to detect upper gastrointestinal tract (UGI) lesions. We aimed to compare MRE and esophagogastroduodenoscopy (EGD) in detecting the spectrum and severity of UGI disease in children.

Methods: This is an ancillary study of the prospective multi-center ImageKids study focusing on pediatric MRE. EGD was performed within 2 weeks of MRE (at disease onset or thereafter) and explicitly scored by SES-CD modified for the UGI and physician global assessment. Local and central radiologists scored the UGI region of the MRE blinded to the EGD. Accuracy of MRE compared with EGD was examined using correlational coefficients (r) and area under receiver operating characteristic curves (AUC).

Results: One hundred and eighty-eight patients were reviewed (mean age 14 ± 1 years, 103 [55%] boys); 66 of 188 (35%) children had macroscopic ulcerations on EGD (esophagus, 13 [7%]; stomach, 34 [18%]; duodenum, 45 [24%]). Most children had aphthous ulcers, but 10 (5%) had larger ulcers (stomach, 2 [1%]; duodenum, 8 [4%]). There was no agreement between local and central radiologists on the presence or absence of UGI inflammation on MRE (Kappa $= -0.02$, $P = 0.71$). EGD findings were not accurately detected by MRE, read locally or centrally ($r = -0.03$ to 0.11, $P = 0.18–0.88$; AUC $= 0.47–0.55$, $P = 0.53–1.00$).No fistulae or narrowings were identified on either EGD or MRE.

Conclusions: MRE cannot reliably assess the UGI in pediatric CD and cannot replace EGD for this purpose.

Key Words: esophagogastroduodenoscopy, imaging, inflammatory bowel disease

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What Is Known

- Lesions are present in the upper gastrointestinal tract in a significant proportion of children with Crohn disease.
- Identification of upper gastrointestinal tract lesions may change the diagnostic label from ulcerative colitis to Crohn disease for 9% to 20% of patients.
- Magnetic resonance enterography accurately identifies inflammation in the small intestine and is recommended for all newly diagnosed children with inflammatory bowel disease.

What Is New

- Upper gastrointestinal lesions seen endoscopically are not accurately detected by magnetic resonance enterography.
- Lesions reported by radiologists on magnetic resonance enterography are not reliably related to mucosal lesions seen endoscopically.

Crohn disease (CD) is a panenteric disease, which can affect any part of the gastrointestinal tract from the mouth to anus. Upper gastrointestinal tract (UGI) inflammation is present in a significant portion of children. Reported prevalence of macroscopic UGI changes ranges from 30% to 64% using very heterogeneous definitions (1). Histopathological changes are present in the UGI tract in 70% to 90% of patients (2–6), with granulomas being

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identified in 2% to 30% (7–9). However, when limiting the definition of UGI disease to only frank ulcerations, and excluding more commonly reported findings of erythema, edema and erosions, prevalence seems to be in the range of 11% to 13% (8,9).

Detecting UGI disease may be the only feature that distinguishes CD from ulcerative colitis (UC) in colonic inflammatory bowel disease (IBD) and aids in the diagnosis when the disease is limited to the upper part of the gastrointestinal tract. In fact, esophagogastroduodenoscopy (EGD) has been reported to impact diagnosis in 9% to 20% of cases (4,9,10). The Porto criteria mandate EGD as part of the initial evaluation in all patients with pediatric CD (11). EGD is, however, invasive, requires anesthesia, and has potential complications.

Magnetic resonance enterography (MRE) provides a non-invasive method to assess inflammation in the gastrointestinal tract (12–15). There are no data, however, on the accuracy of MRE to detect UGI lesions in this population. As an ancillary sub-study of the prospective multi-center ImageKids study, we aimed to compare MRE and EGD in detecting the spectrum and severity of UGI disease in children with CD.

MATERIALS AND METHODS

The ImageKids study (clinicaltrials.gov NCT01881490) aims to create two new MRE-based scoring systems for pediatric CD and to evaluate progression of damage over time. The PICMI (Pediatric Inflammatory Crohn disease MRE Index) will measure inflammation, and the pMEDIC (pediatric MRE Damage Index in Crohn disease) will measure damage. A total of 240 children (<18 years old) with CD have been enrolled in this longitudinal study.

The present study includes data from the first 188 children prospectively enrolled at 21 pediatric IBD centres worldwide between January 1, 2013 and July 28, 2015. Recorded data included demographics, disease characteristics, and prior therapies. Disease activity was captured via the weighted pediatric Crohn disease activity index (wPCDAI) (16).

Children had EGD and MRE performed within a 2-week interval (at disease onset or thereafter), as required for clinical care. Lesions identified on EGD were prospectively scored in the esophagus, stomach, and duodenum by the gastroenterologist at each study site, blinded to the results of the MRE, according to the items of the Simple Endoscopic Score for Crohn disease, modified for the UGI (UGI-SES-CD; Supplemental Figure 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/B234*) (17). We have previously carried out limited validation of the UGI-SES-CD, demonstrating it to correlate with wPCDAI, colonoscopic SES-CD, fecal calprotectin, radiologic global assessment of damage, and serum albumin (18). A physician global assessment (PGA) of inflammation was also scored separately for the esophagus, stomach, and duodenum as: 0, mucosal healing; 1, mild inflammation; 2, moderate inflammation; and 3, severe ulcerating inflammation.

MRE sequences and scoring were standardized across centres (Supplemental Figure 2, Supplemental Digital Content 2, *http://links.lww.com/MPG/B235*). Each protocol included localizer sequences, a motility sequence in the coronal plane, followed by a series of coronal and/or axial rapid T2-weighted, diffusion-weighted and T1-weighted gradient echo sequences. T1-weighted sequences were performed preintravenous and postintravenous gadolinium-based contrast agent (IV GBCA). An intravenous antispasmodic agent (glucagon or hyoscine butylbromide) was also administered following the motility sequence and usually also before IV GBCA. Field of view included from the dome of the liver superiorly to perineum inferiorly. On MRE, the UGI was defined as including the distal esophagus/gastroesophageal junction, stomach, and duodenum to the duodenojejunal flexure.

A radiologist at each enrolling site (a local radiologist), blinded to the EGD results, prospectively completed a standardized MRE report. In their global assessments, they took into account all known signs of inflammation and damage, including enhancement characteristics and T2 hyperintensity of bowel and mesentery, bowel wall thickening, diffusion restriction, bowel motility, fibrofatty proliferation, ulcerations, pseudosacculation, stenoses, abscesses, and fistulae. Severity of inflammatory disease activity (ranging from ''remission'' to ''fulminant''), fistulizing disease (ranging from ''no fistula, and no abscess'' to ''several fistulae and abscesses''), stenosis (ranging from ''no stenosis'' to ''complete obstruction''), and total damage (ranging from ''no damage'' to ''post-resection'') were scored on 100 mm visual analog scales (VAS).

Specifically for this sub-study, central radiologists (two fellowship-trained pediatric radiologists with 10 and 5 years' experience, respectively, reading MRE) re-read a random selection of MRE scans (N = 90 [48%]) using the same criteria, but focusing exclusively on the UGI. This sub-study was performed in order to determine if results from local radiologists may have been influenced by radiologist inexperience identifying UGI disease on MRE. Results from central re-reading would provide the best case scenario for MRE sensitivity in the UGI.

Analysis

Data are presented using medians with interquartile ranges (IQR) or means ± standard deviations according to the distribution. Differences between groups were assessed with the Chi-square test, independent samples *t*-test, or independent samples Mann-Whitney *U*-test as appropriate.

MRE VAS scores from the local radiologists and central radiologists were dichotomized as UGI disease present (MRE VAS > 0) or absent (MRE VAS = 0) and then analyzed using Kappa statistics. Kappa values ≤0.40 were considered poor agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement and ≥0.81 very good agreement (19).

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Correlation between the EGD (measured by the UGI-SES-CD and PGA) and the continuous MRE VAS for inflammation in the esophagus, stomach, and duodenum was sought using Spearman correlation coefficients. Correlation was considered very weak for absolute values between 0 and 0.19, weak for values between 0.20 and 0.39, moderate for values between 0.40 and 0.59, strong for values between 0.60 and 0.79, and very strong for values between 0.80 and 1 (20). Area under the receiver-operating characteristic curve (AUC) was calculated for the ability of the MRE VAS to detect inflammation on EGD as defined by any change, presence of any ulcers, presence of large ulcers (≥ 0.5 cm), and PGA moderate/severe inflammation.

Statistical analyses were performed using SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp). In all analyses, P values < 0.05 were considered significant.

ETHICAL CONSIDERATIONS

This study was approved by the Research Ethics Boards at all institutions participating in the ImageKids study.

RESULTS

MRE and EGD data were reviewed for 188 patients representing a large spectrum of disease duration and severity (Table 1). MRE scans from a random sample of 90 patients were re-read by central radiologists focusing on the UGI. These 90 patients were not significantly different from the rest of the cohort in terms of any baseline characteristics (Table 1). There were also no significant differences in baseline characteristics between those patients with and without UGI disease detected on MRE (data not shown).

The EGD was macroscopically abnormal in 93 of 188 (49%) patients (Table 2). Ulcerations were visible in 66 of 188 (35%), with the duodenum most commonly ulcerated (N = 45 [24%]). A further 27 (14%) patients had other macroscopic abnormalities including nonerosive inflammation or granularity. The UGI-SES-CD scores for inflammation were low (median 0, IQR 0–4, range 0–17), with scores of 0 for 89% in the esophagus, 67% in the stomach, and 70% in the duodenum. Maximum scores were 5 in the esophagus, 7 in the stomach, and 7 in the duodenum. There were no fistulae or narrowings recorded on EGD.

TABLE 1. Patient characteristics at enrollment

Parameter	Total (N = 188)	Central read (N = 90)	P value
Male	103 (55%)	50 (56%)	0.84
Age at diagnosis, years	12 ± 3	12 ± 3	0.77
Age at enrollment, years	14 ± 1	14 ± 2	0.37
Disease duration, years	1.9 (0.0–4.1)	1.9 (0.0–4.0)	0.68
Enrolled at disease onset	55 (29%)	25 (28%)	0.67
Perianal disease	41 (22%)	20 (22%)	0.90
Time between MRE and EGD, days	5 ± 12	5 ± 10	
Prior treatments			
Corticosteroids	94 (50%)	49 (54%)	0.24
Enteral nutrition	68 (36%)	28 (31%)	0.17
5-Aminosalicylates	22 (12%)	11 (12%)	0.83
Thiopurines	77 (41%)	30 (33%)	0.04
Methotrexate	49 (26%)	29 (32%)	0.07
Anti-TNF therapy	64 (34%)	32 (36%)	0.68
Prior surgical resection	9 (5%)	6 (7%)	0.25
Prior UGI surgery	0 (0%)	0 (0%)	n/a
wPCDAI	28 (10–45)	28 (10–48)	0.40
Remission (<12.5)	45 (24%)	24 (27%)	0.40
Mild (12.5–40)	68 (36%)	32 (36%)	0.87
Moderate (40–57.5)	22 (12%)	12 (13%)	0.51
Severe (>57.5)	31 (17%)	19 (21%)	0.10

Count (%), mean ± standard deviation or median (inter-quartile range) are presented as appropriate. EGD = esophagogastroduodenoscopy; MRE = magnetic resonance enterography; TNF = tumour necrosis factor; UGI = upper gastrointestinal tract; wPCDAI = weighted pediatric Crohn disease activity index.

TABLE 2. Upper endoscopy results (N = 188)

EGD change	UGI	Esophagus	Stomach	Duodenum
Any change*	93 (49%)	20 (11%)	63 (34%)	56 (30%)
Ulcers	66 (35%)	13 (7%)	34 (18%)	45 (24%)
Large ulcers	10 (5%)	0 (0%)	2 (1%)	8 (4%)
PGA				
Normal	N/A†	171 (91%)	127 (68%)	133 (71%)
Mild	N/A†	15 (8%)	49 (26%)	37 (20%)
Moderate	N/A†	1 (0.5%)	10 (5%)	12 (6%)
Severe	N/A†	1 (0.5%)	2 (1%)	6 (3%)
UGI-SES-CD				
All	0 (0–4)	0 (0–0)	0 (0–1)	0 (0–1)
Excluding normal segments‡	4 (3–6)	3 (1–3)	3 (1–3)	3 (2–4)

Count (%), or median (inter-quartile range) are presented as appropriate. EGD = esophagogastroduodenoscopy; PGA = physician global assessment; UGI = upper gastrointestinal tract; UGI-SES-CD = simple endoscopic score for Crohn disease of the upper gastrointestinal tract.

*"Any change" was defined by UGI-SES-CD > 0.

†Not applicable. PGA not performed for the UGI as a whole.

‡Median (inter-quartile range) are reported for each anatomical section, only including those patients with detected mucosal abnormalities. N = 93 for the UGI, N = 20 for the esophagus, N = 63 for the stomach, and N = 56 for the duodenum.

The local radiologists identified UGI inflammation in 7 of 188 (4%) patients. Six of these 7 patients had duodenal inflammation, 4 had gastric inflammation, and none had inflammation in the esophagus. The central radiologists identified UGI inflammation in 20 of 90 (22%) patients (6 in the esophagus, 8 in the stomach, and 11 in the duodenum). Only 1 of 20 of these patients was also identified by the local radiologists as having UGI inflammation. There was no agreement between local and central radiologists when examining the UGI as a whole ($\kappa = -0.02$, $P = 0.59$). This was also true when exploring the esophagus ($\kappa = 0$ due to no esophageal disease detected by local radiologists), stomach ($\kappa = 0$ due to no gastric disease detected by local radiologists) and duodenum separately ($\kappa = -0.02$, $P = 0.71$). There were no fistulae or narrowings identified by local or central radiologists on the MRE.

The local radiologists correctly identified only 5 of 93 (8%) patients with UGI findings on EGD. The endoscopic findings included aphthous ulcers in the stomach in 1 patient, aphthous ulcers in the duodenum in 1 patient, and only duodenal erythema in another patient. The remaining 2 patients had large endoscopic ulcers, 1 each in the stomach and duodenum, both correctly localized by the local radiologists. They also incorrectly identified inflammation in an additional 2 patients who had normal EGD findings. Overall, correlation between the MRE and the EGD findings (measured by both UGI-SES-CD and endoscopist PGA) was poor and not statistically significant (Table 3). AUCs for the ability of local radiologists to detect any kind of EGD change, whether defined as any change, ulcers, large ulcers, or moderate/severe PGA was very poor (Table 4).

The central radiologists correctly identified 9 of 45 (20%) patients with UGI findings on EGD. Seven patients had duodenal

TABLE 3. Correlation between inflammation detected by esophagogastroduodenoscopy and magnetic resonance enterography

EGD change	Local radiologists (N = 188)	*P* value	Central radiologists (N = 90)	*P*
Esophagus				
UGI-SES-CD	N/A*	N/A*	0.04	0.72
EGD PGA	N/A*	N/A*	0.05	0.63
Stomach				
UGI-SES-CD	−0.03	0.68	0.11	0.31
EGD PGA	−0.03	0.71	0.09	0.41
Duodenum				
UGI-SES-CD	0.07	0.32	0.03	0.81
EGD PGA	0.10	0.18	0.02	0.88

Inflammation on EGD was measured by simple endoscopic score for Crohn disease of the upper gastrointestinal tract (UGI-SES-CD) and physician global assessment (EGD PGA). Inflammation assessed on MRE was scored by global assessment on a 100 mm visual analog scale ranging from ''remission'' to ''fulminant.'' EGD = esophagogastroduodenoscopy, EGD PGA = physician global assessment of EGD, MRE = magnetic resonance enterography, UGI-SES-CD = simple endoscopic score for Crohn disease of the upper gastrointestinal tract.

*No esophageal disease detected on MRE by the local radiologists.

TABLE 4. Area under the receiver-operating characteristic curves for local and central magnetic resonance enterography reads in detecting upper gastrointestinal tract inflammation based on different endoscopic reference standards

EGD findings	Local radiologists (N = 188)	*P* value	Central radiologists (N = 90)	*P*
Esophageal disease				
Any change	0.50	1.00	0.51	0.90
Any ulcers	0.50	1.00	0.52	0.78
Large ulcers (≥0.5 cm)	N/A*	N/A*	N/A*	N/A*
EGD PGA moderate/severe	0.50	1.00	0.48	0.94
Gastric disease				
Any change	0.50	0.91	0.51	0.78
Any ulcers	0.49	0.81	0.49	0.88
Large ulcers (≥0.5 cm)	0.49	0.96	0.48	0.92
EGD PGA moderate/severe	0.49	0.90	0.52	0.79
Duodenal disease				
Any change	0.51	0.75	0.51	0.88
Any ulcers	0.51	0.86	0.51	0.93
Large ulcers (≥0.5 cm)	0.55	0.64	0.54	0.73
EGD PGA moderate/severe	0.55	0.53	0.47	0.65

Inflammation assessed on MRE was scored by global assessment on a 100 mm visual analog scale ranging from ''remission'' to ''fulminant.'' EGD = esophagogastroduodenoscopy, EGD PGA = physician global assessment of EGD;

*No large esophageal ulcers detected on EGD.

disease—2 had large ulcers (only 1 correctly identified on MRE), 3 had aphthous ulcers (2 of 3 correctly identified on MRE) and 2 had only mild nonulcerative changes to the mucosa (1 of 2 correctly identified on MRE). Four patients had gastric disease on EGD—1 with aphthous ulcers (correctly identified on MRE) and 3 with nonulcerative changes (2 of 3 identified on MRE). There were 2 cases with esophageal aphthous ulceration on EGD with 1 of 2 identified on MRE.

Eleven patients were thought by the central radiologists to have UGI disease on MRE, but had normal EGD. The median VAS scores for the amount of inflammation in the esophagus, stomach, and duodenum were low (0 [IQR 0–14], 10 [IQR 0–19], and 0 [IQR 0–12], respectively) and were not significantly different compared with the 9 patients with confirmed EGD disease. As with local radiologists, there was no correlation between MRE and EGD findings (measured by UGI-SES-CD and EGD PGA; Table 3). The central radiologists could not accurately detect EGD inflammation by any measure with AUCs ranging from 0.47 to 0.55, $P = 0.53$ to 1.00 (Table 4). This was even true of large ulcers seen on EGD, where AUCs for local and central radiologists ranged from 0.48 to 0.55, $P = 0.64$ to 0.92.

DISCUSSION

This is the first report of MRE being used to assess the UGI in either children or adults with CD. We have shown that the ability of MRE to detect UGI disease is very poor and that inter-radiologists agreement is similarly poor. Changes seen on EGD were appropriately identified in only 5 of 93 (8%) patients by local radiologists. Many patients had significant inflammation seen on EGD but no changes seen on MRE. This is true even when the radiologists were asked to pay special attention to the visible esophagus, stomach, and duodenum. EGD should continue to be part of the evaluation for UGI disease in all patients with pediatric CD, as MRE cannot reliably assess the presence of inflammation in this region.

Our cohort included 93 of 188 (49%) patients with some UGI macroscopic findings of inflammation on EGD. Only 66 (35%), however, had ulcers, and as few as 10 (5%) had large ulcers ≥0.5 cm in diameter. This fits well in the middle of the range of UGI disease prevalence previously reported as 11% to 64% (4,6–10,21–24).

Our results should be interpreted with some potential limitations in mind. First, the standardized MRE protocols used at all centres are optimized to visualize the terminal ileum (TI), not the UGI, as universally accepted also in clinical practice. Scans are not initiated until adequate distention of the TI is achieved to optimize interrogation of the distal small bowel. Even if, however, scan timing was altered, achieving adequate distension of the esophagus, stomach, and duodenum would still be extremely difficult because of the large volume required and the rapid transit through these organs. Furthermore, this is not performed routinely in clinical practice. Second, it would be unreasonable to expect MRE to detect most upper GI disease, as it is often mild—only 10 of our patients had large ulcers. Even these large lesions, however, were not detected. Third, the smaller field of view on MRE limited the extent of the esophagus able to be assessed compared with EGD. Fourth, MREs were performed using MRI scanners of different field strengths (1.5 and 3 T) and from a variety of vendors. Similarly, there was some variation between study sites in choice, timing, and delivery of antispasmodic agent and IV GBCA used. These factors, however, have been shown to not affect the accuracy of MRE in detecting inflammation in CD (12), and we did standardize the MRE protocol in all the centres. Lastly, endoscopic assessments were performed by local gastroenterologists, and not by central readers. There was, therefore, likely some degree

of inter-observer variation in scoring that could account for some degree of lack of correlation with MRE. Local gastroenterologists, however, were all experts in pediatric IBD, and they were provided with the schema in Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/MPG/B234, which was not felt to require any specific training.

The excellent overall performance of MRE in assessment of intestinal inflammation has been well established, and it is comparable with other cross-sectional imaging modalities (13). MRE protocols are usually designed to optimize the interrogation of the distal small bowel, since that is where CD is most prevalent. MRE, however, is also an accurate and reliable method to assess the small bowel distal to the duodenum (25). Endoscopy is a more sensitive method for detecting mild ulceration (26), but the jejunum can only be accessed by capsule endoscopy, push enteroscopy, or double-balloon enteroscopy. These methods carry additional risk and are unavailable at many centers. MRE, therefore, remains a safe, accurate, and available modality for detecting small bowel disease distal to the duodenum.

Thorough examination of the UGI has been found to be important in the management of pediatric IBD. The presence of UGI disease may make the diagnosis of CD clear in a case which may otherwise be labelled IBD unclassified (IBD-U). Lesions in the UGI are sometimes hard to interpret, as many cases of UC will have mild changes present (2,27–29). Large ulcers and the presence of granulomas are, however, indicative of CD (3,30).

There are several studies, which have attempted to quantify the diagnostic yield of EGD in pediatric IBD. In the first prospective study to examine this, 11 of 54 (20%) patients had a diagnosis of CD established based on granulomas detected on EGD (4). In another prospective study, granulomas were discovered on EGD, but not ileocolonoscopy, in 12 of 56 (21%) children investigated for IBD (31). A third prospective study including all Hungarian patients diagnosed with IBD over 2 years, reported 16 of 176 (9%) patients with colitis had the ultimate diagnosis of CD established with the help of characteristic EGD findings, including ulcers, cobblestoning, and granulomas (9). Some of these patients, however, might have also had pathognomonic findings of CD in the ileum or colon, so the true yield was likely <9%. Hummel et al (10) retrospectively examined 104 patients with IBD, and they similarly reported 8 (11%) whose diagnosis of CD was based on UGI biopsies. In 5 of 8 cases, this was because of detection of granulomas not found in other parts of the GI tract.

Detection of UGI disease is important as it can impact clinical decision-making. Simply recognizing a diagnosis of CD would push many clinicians to use immune suppressive maintenance therapies, instead of 5-ASA or sulfasalazine. Additionally, sulfasalazine and most 5-ASA preparations release their active compound in the distal ileum and colon, and are, therefore, likely ineffective in the UGI. Also, some may prefer to treat patients with gastroduodenal disease aggressively with anti- tumour necrosis factor (TNF) therapy, which has been shown to be as effective in the UGI as other parts of the GI tract (32), in order to avoid the disastrous complications of duodenal stricture or gastric outlet obstruction.

CONCLUSIONS

The Porto criteria mandate the performance of EGD for all pediatric patients suspected of having IBD. Our study has demonstrated that MRE cannot be relied upon as the sole method of evaluating the UGI. EGD should still be performed in all children and adolescents with suspected IBD in order to obtain biopsy samples and to detect the typically mild mucosal lesions present in the upper GI tract.

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