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MR Enterography in paediatric patients with obscure gastrointestinal bleeding

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A R T I C L E I N F O

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A B S T R A C T

Objectives: To evaluate the performance of Magnetic Resonance enterography (MRE) in the diagnostic work-up of children presenting with obscure gastrointestinal bleeding (OGIB).

Materials and methods: From January 2014 to January 2016, a single-centre prospective study was performed on all children between 0 and 16 years of age referred to the radiology department for OGIB. Each child underwent MRE examination after negative oesophagogastroduodenoscopy and ileocolonoscopy. MRE results were recorded. All patients proceeded to the related gold standard for diagnostic confirmation.

Results: 25 patients (mean age 10.8 ± 4.5 years, range 4 months to 16 years) were included. MRE was diagnostic in 76% (19 of 25). The most frequent diagnoses were intestinal polyp (28%) and Meckel's diverticulum (16%). Sensitivity and specificity of MRE were 86% and 100% respectively. There were no reported complications during any of the examinations.

Conclusion: MRE is a safe and accurate imaging modality in the evaluation of paediatric OGIB. Its diagnostic capability is comparable to current evidence for capsule endoscopy in this patient group. Further research with larger sample sizes and standardized control groups is warranted to improve our understanding of MRE in this application.

1. Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent bleeding or presence of iron deficiency anaemia after negative evaluation with upper and lower endoscopy [1]. OGIB can be subclassified into two clinical forms: obscure-occult, characterised by recurrent iron deficiency anaemia and/or recurrent positive faecal occult blood test, and obscure-overt, which features recurrent passage of visible blood with melena or haematochezia [1].

Although OGIB accounts for only a small proportion of gastrointestinal bleeding in paediatric patients, it represents a particular challenge for clinicians, with consequent risk of delayed diagnosis and high morbidity and mortality. The aetiology ranges from conditions best managed medically or endoscopically (e.g. inflammation, small vascular malformations, and polyps) to those that require a surgical approach (e.g. Meckel's diverticula, intestinal duplications, and large vascular lesions). Accurate and prompt diagnosis is therefore fundamental to expedite management.

Current adult guidelines recommend capsule endoscopy (CE) as the first-line diagnostic investigation for OGIB [2,3], and this modality has also been used for the same indication in paediatric populations [4,5]. However, CE is expensive, time-consuming, and associated with the risk of capsule retention. Due to the uncontrolled nature of the capsule's transit, localisation of the lesion can be problematic, while residual intestinal content, motility disorders, or massive bleeding with clots may impair adequate visualization of the ileal lumen [6,7]. Furthermore, specific data on the diagnostic yield of CE in the evaluation of paediatric OGIB remains scarce, despite numerous reports on its use in

Abbreviations: MRE, magnetic resonance enterography; MR, magnetic resonance; OGIB, obscure gastrointestinal bleeding; CE, capsule endoscopy; IBD, inflammatory bowel disease; TP, true positive; TN, true negative; FN, false negative; PEG, polyethylene glycols; CI, confidence interval

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small bowel disorders [8–11]. Current European Society of Gastrointestinal Endoscopy (ESGE) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) do not definitively suggest routine use of CE in children with acute OGIB [12].

Magnetic resonance enterography (MRE) is now a preferred imaging modality in the study of children with small bowel disease, and may provide an alternative to CE in this context. Unlike CE, MRE enables visualization of the entire transmural aspect of the bowel wall, as well as extraintestinal abnormalities. It carries a comparatively lower cost, with Italian data estimating MRE and CE cost €506 and €1195 respectively [13]. It may also improve detection of Meckel's diverticula, intestinal duplications, and polyps of the small bowel. Such pathologies tend to occur more frequently in paediatric populations as compared to adults [14–16] and for this reason, we believe it may be beneficial to perform MRE before proceeding to CE when assessing paediatric OGIB presentations. Nevertheless, there remains a paucity of concrete evidence surrounding the paediatric applications of MRE beyond inflammatory bowel disease (IBD). The aim of this prospective study is therefore to evaluate the effectiveness of MRE in the diagnostic and therapeutic work-up of children with OGIB.

2. Methods

2.1. Patients

We prospectively enrolled all paediatric patients (defined as age 0–16 years) referred to our unit for OGIB between January 2014 and January 2016. All patients were referred from the paediatric gastroenterology inpatient department of the same institution. All parents or caregivers were briefed in detail about the nature of the procedures. The study was approved by the local ethical committee.

Inclusion criteria were: negative result at oesophagogastroduodenoscopy and ileocolonoscopy; MRE within 20 days of initial endoscopic investigation; follow-up with surgery, enteroscopy, lymph node biopsy, or angiography (gold standard); and parental/caregiver consent. Exclusion criteria were: contraindication to MR; and active bleeding with haemodynamic instability requiring emergent angiography.

Post-MRE, all patients proceeded to the related gold standard for diagnostic confirmation. Resolved OGIB was defined as: (1) no further overt bleeding, (2) haemoglobin level > 10 g/dL at final examination, and (3) no transfusion and no iron replacement within the 6-month period following the final examination.

The primary outcome was the diagnostic yield of MRE for gastrointestinal lesions causing OGIB. MRE was considered diagnostic if the specific diagnostic findings on MRE corresponded to findings from the gold standard diagnostic tool (surgery, enteroscopy, lymph node biopsy, or angiography). All MRE results that showed a gastrointestinal lesion corresponding to OGIB and confirmed on the relevant gold standard tool were considered true positives (TP). If initial MRE did not yield a specific diagnosis but lesions were found on subsequent diagnostic investigations, this was considered a false negative (FN). If initial MRE did not yield a specific diagnosis, and follow-up testing was negative or there was spontaneous resolution of bleeding according to the definition above, the subject was considered a true negative (TN).

2.2. MR enterography technique

All MRE examinations were performed using a 1.5 Tesla (T) whole-body MR unit (Siemens Medical Solution, Malvern, PA, USA) with an eight-channel abdominal phased-array coil. The breath hold technique, and the importance of achieving optimal bowel loop distension were explained to patients and parents. Patients were fasted for 4 hours. 90 minutes before the examination, they were instructed to drink Macrogol 4000 (LOVOL-esse, SIIT Srl, Trezzano, Italy), a polyethyleneglycol (PEG)-water solution with a taste of lemon (dose: 10 mL/kg body weight). If the child was unable to drink the entire dose of oral contrast, we asked them to drink water or juice (or a mixture of both) according to the child's preference in order to reach the target volume of enteric fluid. The child was asked to lie in the right lateral position 10 min before the exam, to facilitate gastric emptying. The examination was then performed with the patients lying prone.

MRE was performed according to the parameters shown in Table 1. Before acquiring MR images, 10 mg of hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Germany) was administered intravenously to reduce SB peristalsis and prolong SB distension.

2.3. Image interpretation

Two certified gastrointestinal radiologists (E.C. and G.M., with fifteen and ten years of experience respectively) independently reviewed MR images on the PACS viewing station (Kodak Carestream; Kodak,

Table 1
Parameters of Pulse Sequences for MRE.

Parameter	True fast-imaging sequence (True FISP)[a]		T2 Half-Fourier sequence (HASTE)[b]		T1 3D sequence (VIBE)[c]	
	Axial	Coronal	Axial	Coronal	Coronal	Axial
Repetition time/echo time (msec)	3.31/1.36	3.51/1.41	800/85	800/87	4.27/1.56	4.35/1.61
Flip angle (degrees)	60	60	120	120	10	10
Field of view (mm)	320–400	320–400	320–400	430	320–400	320–400
Matrix	256 × 192	320 × 270	320 × 216	384 × 256	256 × 256	256 × 192
Parallel imaging factor	2	No/2	2	2	3	2
Section thickness (mm)	4–5	4–5	4–5	4–5	3	3
Intersection gap (mm)	0.9 – 1	0	0.9 – 1	0	0	0
No. of sections per stack	35	20–24	35	20–24	40	72
Breath-hold time per stack (sec)	20 – 15	18 – 10	20 – 15	16	21 – 18	17
No. of stacks	2–3	1	2–3	1	1	2

[a] The true fast imaging sequence is the true fast imaging with steady-state free precession sequence.

[b] The T2 half-Fourier sequence is the T2-weighted half-Fourier acquisition single-shot turbo spin-echo with fat saturation sequence. Fat saturation was achieved with the chemical shift–selective fat suppression technique.

[c] The T1 three-dimensional (3D) fat saturated sequence is the T1-weighetd dynamic volumetric interpolated breath-hold examination (VIBE) with fat saturation sequence. Dynamic T1-weighted imaging was performed with coronal images obtained before contrast agent administration, coronal images obtained in the arterial phases, coronal and axial images obtained in the venous phases, and coronal images obtained in the delayed phase (0.1 mmol/kg gadopentetate dimeglumine [Dotarem; Guerbet, Paris, France] as a bolus, at a rate of 2 mL/s, followed by bolus-injection of 20 mL isotonic saline). Fat saturation was achieved with the chemical shift–selective fat suppression technique or frequency-selective adiabatic inversion pulse (SPIRE).

Rochester, NY, USA). The radiologists were blinded to all clinical information other than the presence of OGIB. Any discrepancies in findings were then discussed and resolved by consensus

The SB was divided into three distinct segments: jejunum, proximal ileum, and distal ileum [17]. The reviewers used four-point visual scales to grade the degree of motion artifact (0, non-diagnostic images; 1, diagnostic images with numerous artifacts; 2, diagnostic images with few artifacts; 3, diagnostic images without artifacts) and bowel segment distension (0, no distension; 1, poor distension; 2, good distension; 3, optimal distension).

The reviewers were asked to evaluate the presence of mucosal findings, focal or diffuse bowel wall thickening, bowel wall enhancement and/or oedema, masses, and perienteric abnormalities (such as mesenteric fat infiltration, hyperemia or standing; abnormal fluid; and abdominal lymph nodes).

2.4. Statistical methods

All data was collated and descriptive statistics performed using the program SPSS (version 23, Chicago, IL). All results were expressed as raw percentages or mean ± 1 standard deviation.

Table 3
Image quality assessment.

Degree of motion artifact, n, (%)	
Grade 0	0 (0%)
Grade 1	3 (12%)
Grade 2	11 (44%)
Grade 3	11 (44%)
Degree of bowel distension at jejunum, n, (%)	
Grade 0	4 (16%)
Grade 1	5 (20%)
Grade 2	8 (32%)
Grade 3	8 (32%)
Degree of bowel distension at proximal ileum, n, (%)	
Grade 0	0 (0%)
Grade 1	1 (4%)
Grade 2	8 (32%)
Grade 3	16 (64%)
Degree of bowel distension at distal ileum, n, (%)	
Grade 0	0 (0%)
Grade 1	3 (12%)
Grade 2	8 (32%)
Grade 3	14 (56%)

3. Results

The final study population consisted of 25 patients, 14 male and 11 female (mean age 10.8 ± 4.5 years, range 4 months–16 years). 12 patients had an overt-type OGIB, and 13 had occult OGIB. Pre-procedure haemoglobin was 7.6 ± 1.2 g/dL (range 3.5-9.9). Baseline patient characteristics are presented in Table 2.

3.1. Image quality assessment

22 of 25 MRE examinations (88%) yielded images with little or no motion artifact (grade 2 or 3) (Table 3). There was good or optimal bowel distension in 64%, 96%, and 88% at the jejunum, proximal ileum, and distal ileum respectively (Table 3).

3.2. MRE findings

19 of 25 MRE examinations demonstrated positive results (Table 4). Of these, 9 had overt-type OGIB (Fig. 1). MRE accurately identified and localized all 7 polyps (dimension range: 1.8–5 cm) later confirmed on surgical or enteroscopic examination, including two with signs of intussusception (Fig. 2). It was similarly able to diagnose all 4 Meckel's diverticulum cases (Fig. 3). The MRE features of Crohn's disease have been well-described. In our study, characteristics including thickening of the bowel wall, dilation of the mesenteric vasculature, and adjacent lymphadenopathy assisted in the diagnosis of Crohn's disease in two cases. MRE was also able to detect more unusual sources of OGIB, including a giant jejunal hemangioma in a 6-year-old girl with anaemia and syncope (Fig. 4), enteropathy associated T-cell lymphoma in a 12-year-old girl, and angiomatosis in a 4-month-old girl.

MRE was negative in 6 of 25 patients (Table 5). Of these, 3 had occult-type OGIB.3 of these cases were true negatives and no further pathology was visualized on subsequent surgical evaluation. MRE was falsely negative in 3 cases; two of which were later diagnosed with angiodysplasia and one with ileal anastomotic ulcers.

Table 2
Patient characteristics.

Total number of patients	26
Age (years), mean ± SD[a] (range)	10.7 ± 4.4 (0.33–16)
Sex (M/F)	14/12
Type of OGIB, n, (%)	
Obscure-occult	13 (50%)
Obscure-overt	13 (50%)
Blood haemoglobin level (g/dL)[b], mean ± SD, range	7.6 ± 1.2 g/dL (3.5–9.9
Previous abdominal surgery, n, (%)	3 (11.5%)
Accompanying symptoms	
Abdominal pain	9 (34.6%)
Diarrhea or constipation	2 (7.7%)
Weight loss and/or slow growth	2 (7.7%)
Vomiting	1 (3.8%)

[a] SD: standard deviation.
[b] Blood haemoglobin level measured within a median of 14 days (range 3–42) before MRE.

3.3. Diagnostic performance

Overall, MRE was diagnostic in 19 of 25 examinations (76%). There were 3 FN results in which MRE was negative but later enteroscopy or surgery identified a pathological source of OGIB. 100% of patients were followed up with gold standard diagnostic testing (enteroscopy, surgery, lymph node biopsy, or angiography). Overall sensitivity and specificity were 86% (95% CI = 65–97%)and 100% (95% CI = 29–100%), respectively. There were no complications reported during any of the MRE examinations.

4. Discussion

MRE is an increasingly important paediatric imaging modality and is currently a first-line imaging investigation for assessing the extent of IBD [18], being particularly preferred in children as it eliminates exposure to ionizing radiation [19–21]. Though anecdotal evidence suggests that MRE is potentially useful in studying small bowel pathologies beyond IBD [22,23], supporting data remains scarce. Our study is the first to evaluate MRE as an imaging tool in the diagnostic work-up of paediatric OGIB. Our results indicate that MRE has a diagnostic yield (73%) which is comparable to results achieved by CE in the same application. In a recent multicentre European study, CE was able to identify a source of bleeding in 16 of 30 paediatric patients with OGIB (53%) [10]. Older studies of CE with much smaller populations of fewer than 10 paediatric patients with OGIB report higher rates [8,9,11]. Of note, MRE was able to detect a broad spectrum of pathologies causing OGIB. MRE identified and localized all small bowel masses, including seven polyps and one giant jejunal hemangioma, allowing these patients to proceed expeditiously to enteroscopy or direct laparoscopy. By

Table 4
Findings in patients with positive MRE result.

Patient number	Type of OGIB	Finding on MRE	Final diagnosis	Reference standard
1	Overt	5 cm polyp in jejunum	Jejunal polyp	Enteroscopy
2	Overt	2 cm polyp in jejunum	Jejunal polyp	Enteroscopy
3	Occult	3 cm polyp in jejunum Intussusception	Jejunal polyp Intussusception	Surgery
4	Overt	1.8 cm polyp in proximal ileum	Ileal polyp	Enteroscopy
5	Occult	2 cm polyp in proximal ileum	Ileal polyp	Surgery
6	Occult	2.5 cm polyp in proximal ileum Intussusception	Ileal polyp	Surgery
7	Occult	2 cm polyp in proximal ileum	Ileal polyp	Surgery
8	Overt	1.2 cm Meckel's diverticulum (blind pouch with wall enhancement) in distal ileum	Meckel's diverticulum	Surgery
9	Overt	2.6 cm Meckel's diverticulum (blind pouch with wall enhancement) in distal ileum	Meckel's diverticulum	Surgery
10	Overt	2 cm Meckel's diverticulumin distal ileum (blind pouch with wall enhancement)	Meckel's diverticulum	Surgery
11	Occult	6 × 3.5 cm polyp in jejunum	Jejunalangioma	Surgery
12	Occult	Intestinal lymphoma (mesenteric lymph nodes ranging 0.5–4 cm in dimension, with thickening of the wall of the distal ileum and hepatosplenomegaly)	Enteropathy associated T-cell lymphoma	Lymph node biopsy
13	Occult	Intussusception Mesenteric adenopathy Atonic intestinal loops	Intussusception	Surgery
14	Occult	Intussusception	Intussusception	Surgery
15	Overt	Diffuse intestinalangiomatosis Retroperitoneal DVT	Angiomatosis	Angiography
16	Overt	Crohn's disease of the proximal ileum (proximal ileum loop thickening with stratified appearance after contrast media, vasa recta sign)	Crohn's disease	Enteroscopy(with biopsy)
17	Occult	Crohn's disease of the jejunum (layered and symmetric thickening of the jejunal loop wall, T2 submucosal edema, comb sign, mesenteric lymphadenopathy)	Crohn's disease	Enteroscopy(with biopsy)
18	Occult	Non-specific thickening of jejunal and ileal wall Mesentericlymph-adenopathy	Spontaneousresolution of symptoms	Enteroscopy
19	Overt	Meckel's diverticulum in distal ileum (blind pouch with wall enhancement)	Meckel's diverticulum	Surgery

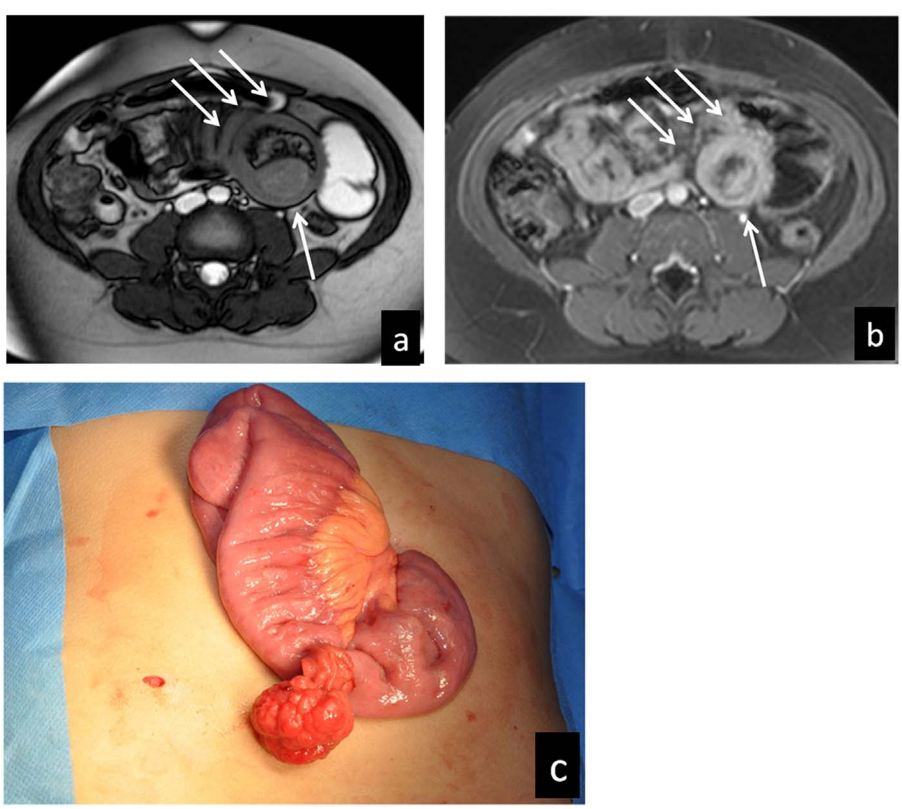

Fig. 1. Polyp with intussusception in a 7-year-old child with anaemia and occult-type OGIB.
Transverse TRUE FISP (a) and dynamic contrast-enhanced T1 fat saturation (b) MR images show a jejunal intussusception (arrows) due to a polyp (single arrow). The polyp was subsequently removed laparoscopically (c), instead of with balloon-assisted enteroscopy, because of the MRE result showing intussusception.
Colour should be used for c

Fig. 2. Meckel's diverticulum in a 10-year-old child with bloody painful stool. Transverse T2 HASTE (a) and coronal TRUE FISP(b) images show a small mass (arrow) in the right lower segment of the ileum, with clear boundaries and heterogenous signal enhancement consistent with Meckel's diverticulum. Diagnosis of Meckel's diverticulum was confirmed at surgery (c).
Colour should be used for c

detecting any associated intussusception, MRE was also able to guide safe therapeutic decision-making (laparoscopy instead of balloon-assisted enteroscopy). MRE diagnosed two cases of Crohn's disease, both of which were limited to the small bowel. Isolated small bowel Crohn's disease is frequently underdiagnosed and is associated with a more complicated disease course, with early development of strictures and fistulas [24–26]. Prompt identification of these cases with tools such as MRE may therefore inform more aggressive management strategies with subsequent patient benefit [27].

Nevertheless, MRE is not without its challenges. Patients must be thoroughly prepared prior to examination in order to obtain images of the appropriate quality. Appropriate breath-holding technique, along with the ability to tolerate both oral and IV contrast are critical to a successful MRE examination, and may be difficult for younger patients. In our experience, flavouring the oral contrast (Macrogol 4000) with lemon, and providing patients and parents with comprehensive pre-procedure education were effective in acquiring high-quality images. As a last resort, the examination may be performed under general anaesthesia (1 of our patients). This patient received anaesthesia on the MR table, and the small bowel was filled by manual injection through a fluoroscopically-placed nasojejunal tube.

Motion artifact was minimal (grade 1 in 3 patients only; grade 0 in no patients), and ileal bowel distension was good or optimal in 88–96% of patients. We noted a lower degree of jejunal bowel distension (good or optimal in 65%). This may be due to lengthy bowel preparations, starting from 90 min pre-procedure. Others have experienced similar problems. In their study of 58 paediatric patients, Sieczkowska et al. reported 21.1% as having insufficient distension of earlier bowel loops, compared to 5.2% in the terminal ileum [28]. Using shorter preparation times and staggering preparations may help improve jejunal distension. In one suggested approach in adults, the patient drinks 1-1.5L of PEG solution at 60 min before imaging, then 250 mL at 30 min before imaging, another 250 mL at 15 min before imaging and then 500 mL of water immediately before imaging [29]. A similar approach with modified volumes might be useful in children.

In our study, MRE also appeared to struggle to identify small lesions such as superficial ulcers and angiodysplasias. False negative results occurred in 3 patients, two affected by angiodysplasia and one with ileal anastomotic ulcers. Subsequent CE correctly identified all these lesions, although one case required second-look CE examination. Evaluation of early, superficial, or subtle mucosal abnormalities with MRE remains a challenge in both children and adults due to the low spatial resolution. 3T MR scanning may improve spatial and temporal resolution by increasing the signal-to-noise ratio by approximately 1.7-1.8 times that of 1.5T MR [30,31].

At our institution, the standard approach in children with OGIB is to study the small bowel with SICUS (small intestine contrast ultrasonography) or MRE before CE. This is to optimize patient safety (as performing CE in patients with strictures can be dangerous), and is also in keeping with current European Crohn's and Colitis Organisation guidelines [32]. However, we note that the lack of control group in our study prohibited standardized comparison between MRE and CE, and recommend the need for future research with adequate controls. Our study was also limited by its relatively small sample size, though this is comparable to existing literature around the topic of paediatric OGIB. Evaluation of image quality was subjective and based on the radiologist's impressions. Finally, we acknowledge the bias associated with the way MRE guided our choice of definitive diagnostic investigations in each individual, but note that all patients were followed up for 6 months and no new bleeding occurred in any patient who received surgical or endoscopic intervention.

Despite these limitations, our results suggest that MRE may have a role in the diagnostic work-up of children with OGIB. It offers excellent visualization of both intra- and extraluminal disease in the small bowel.

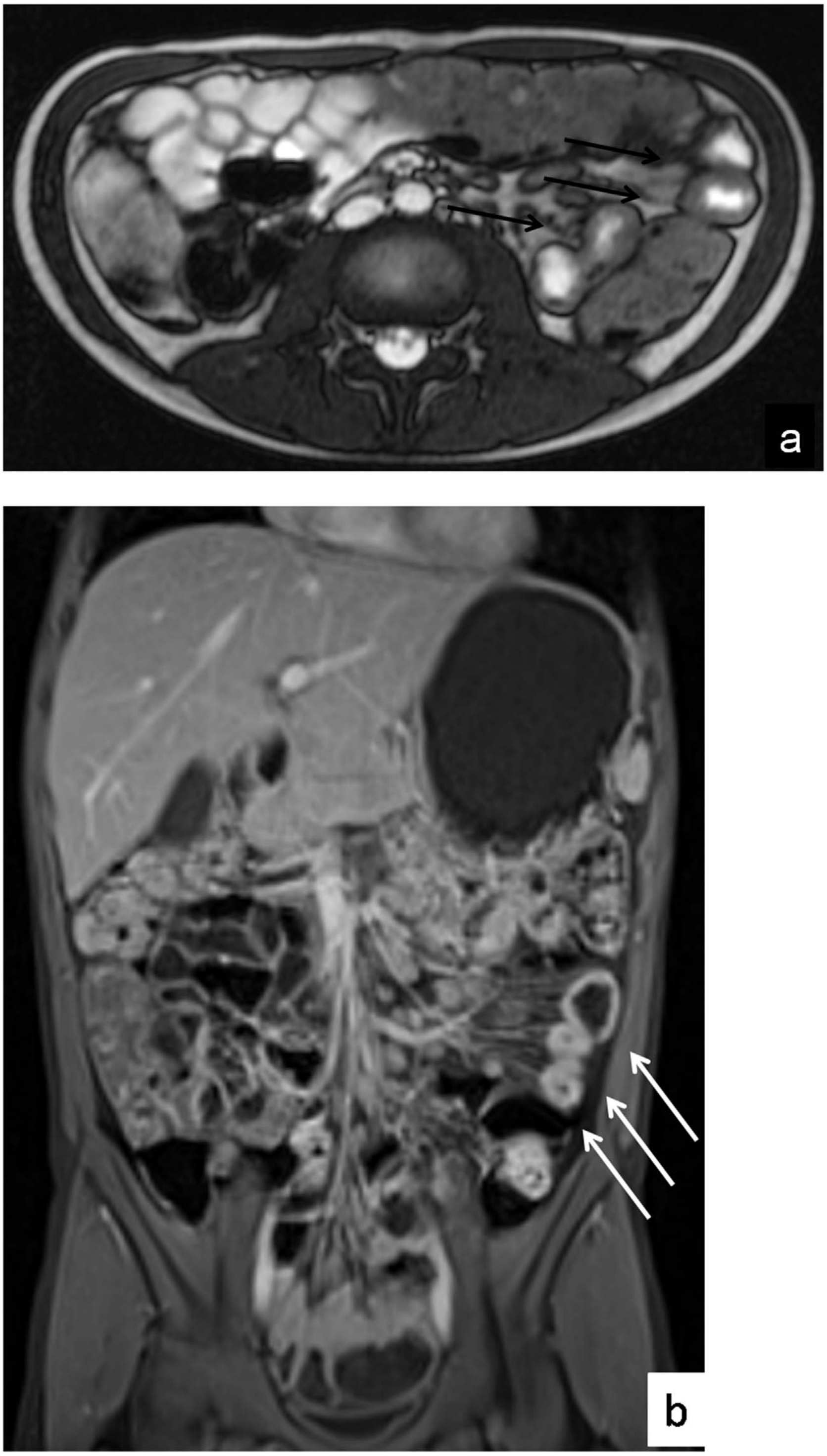

Fig. 3. Crohn's disease in the upper SB walls in a 14-year-old child with abdominal pain and anaemia.
Transverse steady-state (a) shows thickened walls of three concentric jejunal loops (arrows). Coronal T1 3D image after intravenous contrast media (b) shows homogenous and concentric thickening of the jejunal loops (arrows) and increased mesenteric vascularity adjacent to the inflamed bowel loop (the comb sign) with multiple mesenteric lymph nodes.

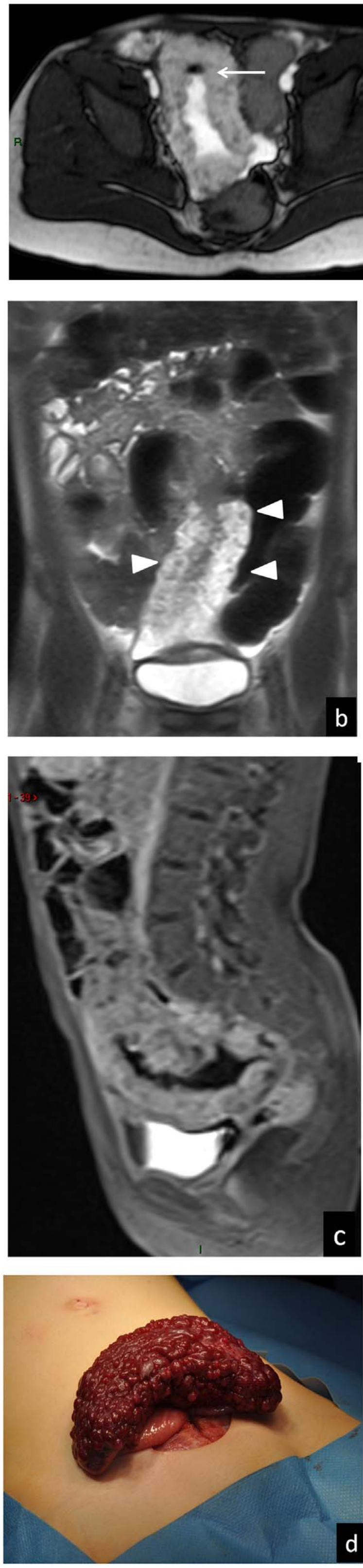

Fig. 4. Jejunal giant cavernous hemangioma in a 6-year-old child with syncope and anaemia (Hb 3.5 mg/dL).
The transverse TRUE FISP (a), and coronal T2 HASTE (b) MR images show a circumferential infiltration of the small-bowel wall which is frankly hyper-intense with fluid content and associated with air bubbles in the lumen (arrow).There are tiny hypo-intense spots (arrowheads) into the thickened wall of the small bowel, consistent with calcification. Sagittal multiplanar reconstruction T1 contrast-enhanced, fat-suppressed during delayed phase (c) images show homogeneous hyper-enhancement of the thickened small bowel wall. Intraoperative photograph (d) shows a circumferential mass composed of large blood-filled spaces, consistent with ajejunal giant cavernous hemangioma.

In our experience, it is a safe and accurate imaging modality, with a diagnostic yield that is comparable to CE. However, CE remains the method of choice in the detection of small mucosal lesions, and further research with larger study populations and standardized control groups is warranted to improve our understanding of MRE in this application.

Table 5
Findings in patients with negative MRE result.

Patient number	Type of OGIB	Finding on MRE	Final diagnosis	Reference standard
1	Occult	Negative	Angiodysplasia of proximal and distal ileum	Enteroscopy
2	Occult	Negative	Angiodysplasia of jejunum Perianastomotic ulcer	Enteroscopy
3	Overt	Negative	Anastomotic ulcer	Enteroscopy
4	Overt	Negative	No pathology	Surgery (laparoscopy)
5	Overt	Negative	No pathology	Surgery (laparoscopy)
6	Occult	Negative	Spontaneous resolution of symptoms	Surgery (laparoscopy)

Competing interest

None to declare.

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