Pediatric inflammatory bowel disease: Diagnostics, treatment and psychosocial consequences
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Accuracy of abdominal ultrasound and MRI for the detection of Crohn’s disease and ulcerative colitis in a pediatric population

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Submitted
ABSTRACT

Objectives: Endoscopy is currently used as primary technique to diagnose inflammatory bowel disease (IBD) in children; its major limitation is the associated burden. The aim of this study was to assess the accuracy of ultrasound and dynamic contrast-enhanced (DCE-)MRI for diagnosing IBD and for distinguishing between Crohn’s disease (CD) and ulcerative colitis (UC).

Methods: Consecutive consenting pediatric patients with suspected IBD were included. Patients underwent diagnostic work-up including ileocolonoscopy and upper gastrointestinal endoscopy under general anesthesia, abdominal ultrasound and MR entero- and colonography at 3T. The protocol included a dynamic contrast enhanced 3D sequence. DCE-MRI parameter maximum enhancement was calculated. Sensitivity and specificity were calculated for one ultrasonographer and two MRI observers.

Results: 28 pediatric patients were included (15 males, mean age 14, range 10-17 years). Diagnosis was CD in 12 patients (43%), UC in 10 patients (38%), indeterminate colitis in one (4%) and five patients did not have IBD (18%). To diagnose IBD, sensitivity and specificity were 55% and 100% for ultrasound, and 57% and 75-100% for MR entero- and colonography, respectively. Combined MRI and ultrasound had a sensitivity of 70-74% and a specificity of 80-100%. With the addition of a DCE-sequence sensitivity increased to 83-87%, specificity 80-100%.

Ultrasound and MRI could only distinguish between CD and UC when terminal ileum lesions were found.

Conclusions: Ultrasound and DCE-MRI can be used to diagnose IBD in a pediatric population but cannot be used to exclude IBD or to differentiate between CD and UC.
INTRODUCTION

Inflammatory bowel disease (IBD) comprises two major disorders: ulcerative colitis (UC) and Crohn’s disease (CD). These disorders have distinct pathologic and clinical characteristics. Patients with colonic disease who cannot be classified into one of these two major forms of IBD are classified as having indeterminate colitis. In pediatric series, the prevalence of indeterminate colitis ranges from 5% to 30% (1).

In children suspected of IBD, it is important to establish the correct diagnosis because there is a difference in treatment strategies of CD and UC. This is done by a diagnostic work-up comprising clinical history, physical examination, laboratory studies, endoscopic findings, histological interpretation of mucosal biopsy specimens and imaging studies. Current guidelines recommend upper and lower tract endoscopy and small bowel Magnetic Resonance Imaging (MRI) (1,2). In most countries, upper and lower endoscopies in children are performed under general anesthesia. Patients are admitted to the hospital for colonic preparation one day before the procedure. Many children do not accept the flavour of the polyethylene glycol electrolyte solution, for which a nasogastric tube is used instead. Imaging techniques are less burdensome and can potentially replace endoscopies.

Abdominal ultrasound is used for diagnosing IBD, with a sensitivity ranging from 48% to 88% and a specificity of 93% for the pediatric population (3-5). Lower sensitivity is due to missed cases when they only have mild disease activity such as erythema of the bowel wall (3). As ultrasound is a non-invasive technique, it is well tolerated by children. Drawback is that deeper situated structures such as the rectum and some anatomic locations such as the upper gastrointestinal tract are more difficult to assess with ultrasound.

Small bowel MRI is increasingly used for diagnosis and assessing disease activity of the small bowel in children with CD (6). Sensitivity in pediatric patients for detecting IBD ranges from 61 to 92% and specificity from 60 to 92% (5,7,8). MRI colonography can be used for diagnostic evaluation of the large bowel, to determine the site and extend of disease and to detect complications. However, the experiences with MRI colonography in pediatric patients are scarce. Dynamic contrast-enhanced (DCE-)MRI is a new MRI method that may further increase the accuracy. DCE-MRI measures the changes in MRI signal intensity during the injection of intravenous contrast. This contrast medium passes from the vasculature into the extravascular-extracellular space and in that way produces parenchymal enhancement. In IBD a marked increase in signal intensity of the actively diseased bowel wall can be seen due to increased vascular permeability of inflammatory tissue (9-11). This could be helpful in the diagnosis of IBD.
The purpose of our study was to assess the accuracy of (DCE-)MR entero- and colonography and abdominal ultrasound for the diagnosis of IBD in comparison to upper and lower tract endoscopy in children suspected for IBD. Our second aim was to determine if MR entero- and colonography and abdominal ultrasound can differentiate between CD and UC.

MATERIALS AND METHODS

Thirty consecutive pediatric patients with suspected IBD were prospectively included in this study from August 2010 to April 2011. They were all scheduled for upper gastrointestinal tract (UGT) endoscopy, ileocolonoscopy, abdominal ultrasound and MR entero- and colonography. Exclusion criteria were age <8 and ≥18 years and general contraindications for undergoing MR imaging (such as metallic implants and claustrophobia). The pediatric ulcerative colitis activity index (PUCAI) (12) and pediatric Crohn’s disease activity index (PCDAI) (13) were determined for all patients at inclusion.

Reference standard

The reference standard procedure consisted of UGT endoscopy, ileocolonoscopy and histopathological interpretation. The diagnosis based on endoscopic findings and histopathology results was established by two pediatric gastroenterologists in consensus. Endoscopy was performed under general anesthesia by an expert pediatric endoscopist, histopathological interpretation was performed by an expert pathologist. The colon was adequately cleansed before endoscopy with Klean-prep (PEG 3350 solution), the amount depending on patient’s weight. Endoscopy was performed using a standard gastro- and colonoscope (Olympus Medical Systems Europe, Hamburg, Germany). In the lower gastrointestinal tract the presence of mild lesions (erythema, friability, exudate, granularity, loss of vascular pattern, aphtae) and severe lesions (ulcerations and cobblestoning) were noted per segment (terminal ileum, cecum and ascending colon, transverse colon, descending and sigmoid colon, and rectum). In addition, tissue sampling was performed in all segments at every 10 cm. In the upper tract biopsies were taken from duodenum, stomach (antrum and corpus) and esophagus. If suspect lesions were present, then these were biopsied; otherwise, random tissue sampling was performed. An endoscopic diagnosis was given by the endoscopist (CD, UC, indeterminate colitis or no IBD).

Histopathology assessment of the terminal ileum and colon was performed according to the modified version of the D’Haens scoring system (score ranges from 0 to 16, higher score indicating more histopathological abnormalities) (14). A score for the terminal ileum was calculated as well as a mean and highest score for the colon.
MR entero- and colonography examination

All MR entero- and colonography examinations were scheduled within five weeks of the endoscopy. Three hours before the MR entero- and colonography patients ingested 400 ml sorbitol (6-9%, concentration depending on age) followed by 400 ml sorbitol 3.5% one hour before the MRI (small bowel preparation). The two volumes of oral contrast were given to ensure both small bowel and large bowel distension. During this period no ingestion of food or other fluids was allowed, with the exception of additional water.

MR entero- and colonography was performed on a 3.0-T MRI scanner (Intera, Philips Healthcare, Best, the Netherlands) using a 16-channel torso phased-array surface coil. T2-weighted single shot fast spin echo (T2 SSFSE), diffusion weighted (DWI) sequence and dynamic coronal 3D T1-weighted fast spoiled gradient echo (SPE) sequence images of the small and large bowel were acquired. The dynamic 3D T1-weighted fast SPE sequence consisted of 450 consecutive scans with a temporal resolution of 0.82 seconds. The dynamic volume was placed on the location of visibly inflamed bowel (on SSFSE images) or when absent the terminal ileum.

Ten seconds after the start of the dynamic sequence 0.1 ml/kg bodyweight of gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) was injected through a intravenous cannula in the antecubital vein by bolus injection (1-5 ml/s, depending on diameter of the intravenous cannula) using an automated injection pump (Mallinckrodt Optistar, Liebel-Flarsheim, Cincinnati, Ohio, USA). Injection of contrast medium was immediately followed by a bolus of 15 or 20 ml saline, depending on the length of the contrast injection tube. After completion of the dynamic sequence coronal and axial post-contrast 3D T1-weighted SPE images were acquired. All scan parameters are given in table 1.

Two doses of ten milligram scopolamine butylbromide (Buscopan, Boehringer, Ingelheim, Germany) were given intravenously, immediately before the DCE-MRI sequence and before the post-contrast 3D T1-weighted SPE sequences.
Table 1. MRI Scan parameters at 3T

<table>
<thead>
<tr>
<th>Sequences</th>
<th>T2 SSFSE sequence</th>
<th>T2 SSFSE sequence</th>
<th>T2 SSFSE sequence</th>
<th>DWI</th>
<th>DCE-sequence</th>
<th>T1 SPE sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction</td>
<td>Axial and coronal</td>
<td>Coronal</td>
<td>Coronal</td>
<td>Axial</td>
<td>Coronal</td>
<td>Axial</td>
</tr>
<tr>
<td>Fat saturation</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TR/TE (ms)</td>
<td>516/65</td>
<td>1450/70</td>
<td>2.19/1.0</td>
<td>5000/40</td>
<td>2.9/1.8</td>
<td>2.19/1.0</td>
</tr>
<tr>
<td>Flip angle (degrees)</td>
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<td>90</td>
<td>10</td>
<td>90</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Slice thickness/gap</td>
<td>4/1</td>
<td>7/1</td>
<td>-</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Slices</td>
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<td>45</td>
<td>100</td>
<td>240</td>
<td>450</td>
<td>180</td>
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<tr>
<td>FOV (mm)</td>
<td>400x400</td>
<td>375x300</td>
<td>375x304</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T2 SSFSE = T2-weighted single shot fast spin echo, DWI = diffusion weighted, DCE = dynamic contrast-enhanced, T1 SPE = T1-weighted fast spoiled gradient echo, TE/TR = echo time/repetition time, FOV = field of view.

DCE-MRI image analysis

DCE-MRI registers change in signal intensity over time during the administration of intravenous contrast medium. To calculate the difference in signal intensity, regions of interest (ROIs) were drawn with software ITK-SNAP (15) on the DCE-sequence by a research fellow on all available slices where the segment was visible. Within the ROIs, lumen and air were subsequently segmented based on isodata thresholding. We performed retrospective gating and registration on the DCE volume (16) to correct for motion caused by patient’s respiratory movements. The first 300 DCE volumes (= 246 seconds) were used for analysis, since peristalsis resumed after this period. In each ROI we calculated the relative maximum enhancement (peak of post contrast signal divided by the baseline signal intensity) and the initial slope of increase (the curve’s differential) on a pixel-by-pixel basis and then averaged across the ROI (17). The DCE-MRI data were analyzed off-line using home-written software and were not included in the conventional MRI assessment.

MR entero- and colonography assessment

MR entero- and colonography assessments were performed by two experienced pediatric radiologists with 12 years (observer 1) and 20 years experience (observer 2). The scoring of the MR entero- and colonography was performed after inclusion had ended (minimum 2 months) because the second observer also performed the ultrasound examination.
Quality of MR entero- and colonography was assessed per segment as good (optimal distension and contrast between lumen and bowel wall), adequate (less than optimal distension and contrast between lumen and bowel wall, but diagnostic) or insufficient (not diagnostic, could not be assessed).

The whole colon and the terminal ileum were assessed. The proximal small bowel was assessed clinically but not included in our analysis because there was no available reference standard data for those lesions.

Diagnosis was based on the presence of the following features: thickened bowel wall (> 3 mm) on T2-weighted images, increased mural T2 signal intensity on T2-weighted images, T1 bowel wall enhancement after intravenous contrast, the presence of layered enhancement, absence of haustrations, presence of peri-colonic mesenteric edema, the comb sign (increased mesenteric vascularity), creeping fat (fibro-fatty proliferation around the bowel wall) and dilatation of the colon or small bowel and diffusion restriction on the DWI sequence. After assessing all parameters a diagnosis (IBD yes/no) was given based on the presence of these parameters. For our second aim, differentiating between UC and CD, the localization of lesions was determined. Continuous lesions from the rectum to proximal were indicative of UC; skip lesions and transmural inflammation were indicative of CD. In addition, transmural disease was more indicative of CD whereas mucosal disease of UC. The two observers gave for each IBD patient a diagnosis of either CD or UC.

**Abdominal ultrasound**

Bowel wall ultrasound examinations were performed by observer 2 or one other pediatric radiologist on the same day as MR entero- and colonography using a Philips IU22 ultrasound unit (Philips Healthcare, Best, the Netherlands) with a linear probe with band frequency of 25-38 Hz and Doppler equipment. Per segment (same as with MRI) the following features were assessed: wall thickness (a thickness >3 mm was considered abnormal), layered appearance of the bowel wall and the presence of abdominal lymphadenopathy. Doppler measurements (the peak systolic velocity, mean diastolic velocity, end-diastolic velocity and resistance index) of the superior and inferior mesenteric arteries were performed. A diagnosis was given based on the presence of all features. Continuous lesions from the rectum to proximal were indicative of UC; skip lesions and transmural inflammation were indicative of CD. As in MRI, the localization of lesions was indicative in distinguishing between CD and UC.

**Power analysis**

We anticipated a sensitivity for diagnosing IBD of 81.8% and 95% confidence intervals of 0.42% (5). To obtain these values, with a power of 0.95 and 2-sided interval, 13 patients with IBD would be required. Based on suspected prevalence of IBD of 50%, 26 patients were needed. Thirty patients were included to account for possible withdrawals.
Statistical analysis
Qualitative data are presented as percentage and quantitative data as mean/median and interquartile range values, depending on distribution. Differences in histopathology scores between groups were tested with the Mann-Whitney U test. Performance statistics (sensitivity, specificity) were calculated for the different imaging modalities: ultrasound and MR entero- and colonography (both observers). We evaluated if the addition of a DCE-MRI sequence to the conventional MRI sequences could further increase accuracy. To calculate the optimal cut-off values to predict IBD for the DCE-MRI parameters (maximum enhancement and initial slope of increase), we performed receiver operating characteristic (ROC) curve analysis. We evaluated the area under the ROC curve (AUC). The best cut-off value was determined by balancing the best combined sensitivity with the lowest false-positive rate. For the DCE analysis, the segment with highest maximum enhancement and highest initial slope of increase were used to determine the cut-off values.

We also calculated ROC graphs for all different imaging strategies and assessed the AUC to determine the best imaging strategy.

We also calculated performance statistics (sensitivity, specificity) for MR entero- and colonography and ultrasound to differentiate between UC and CD.

Kappa values were calculated to assess interobserver variability between the two MRI observers. Values were interpreted as follows: 0.0-0.2 no agreement, 0.2-0.5 weak agreement, 0.5-0.8 moderate agreement, 0.8-1.0 strong agreement and 1.0 perfect agreement. Statistical analysis was performed by using software PASW statistics 18 (Chicago, IL). A p-value <0.05 was considered significant.

Ethical considerations
A research grant was given by Nuts Ohra Foundation. Nuts Ohra Foundation was not involved with study design, collecting the data and writing the manuscript. Ethical permission was obtained by the hospital medical ethics committee. Oral and written informed consent was obtained from all parents and patients (if older than 11 years).
RESULTS

Patient and baseline characteristics
A total of 30 patients were initially included in this study, 2 patients were excluded (one refused to undergo endoscopy and in one patient endoscopy was postponed by >3 months). The final cohort consisted of 28 children with suspected IBD (15 males, mean age 14, range 10-17 years). Based on our reference standard 23 patients were diagnosed with IBD (72%): 12 CD, 10 UC, one indeterminate colitis. Five patients did not have IBD (18%). We excluded the patient with indeterminate colitis from the subgroup analysis (distinguishing CD versus UC) because the subgroup indeterminate colitis would have been too small (N=1). This patient was however included in the IBD analysis.

In patients with CD median PCDAI score was 31 (interquartile range (IQR) 20-39), in patients with UC median PUCAI score was 43 (IQR 29-79). Median time between endoscopy and ultrasound/MR enter- and colonography was 7.5 days (range 1-40). Ultrasound was performed in 24 patients (three exams could not be performed due to logistics and one was incomplete due to high body mass index of the patient). The rectum could not be assessed in 23 patients; all other segments could be evaluated with ultrasound. MR enter- and colonography was performed in 27 patients (one exam failed due to claustrophobia). In six patients the image quality in one or more segments was non diagnostic; three terminal ileum, two transverse colon and two rectum. The DCE volume did not include the following segments, because of the fact that the DCE-volume could not fit all segments: four terminal ileum, five transverse colon, two descending colon and 27 rectum. MRI scoring was performed two to six months after finalizing the inclusion.

DCE cut off value
When performing ROC curve fitting for the DCE parameters maximum enhancement and initial slope of increase, we found an AUC of 0.66 for maximum enhancement and 0.52 for initial slope of increase, showing a relative acceptable performance for maximum enhancement but not for initial slope of increase. For maximum enhancement we found a cut-off value from the ROC curves of 0.40. This value was used to calculate diagnostic accuracy combined with MR entero- and colonography and ultrasound.

Diagnostic accuracy
Based on ultrasound, the diagnosis was IBD in 11 patients (eight CD, three UC) and no IBD in 13 patients. With MR entero- and colonography, diagnosis was IBD in 13 patients (eight CD, five UC) and no IBD in 14 patients for observer 1. For observer 2 diagnosis was IBD, based on MR entero- and colonography, in 14 patients (seven CD, six UC, one indeterminate) and
no IBD in 13 patients. With DCE-MR entero- and colonography, diagnosis was IBD in 17 patients for observer 1 and 18 patients for observer 2. For the diagnosis of IBD, sensitivity was 55% for ultrasound and 57% for MR entero- and colonography (both observers), specificity was 100% for ultrasound and 100% (observer 1) and 75% (observer 2) for MR entero- and colonography (figure 1 and 2). AUC was 0.775 for ultrasound and 0.783 (observer 1) and 0.658 (observer 2) for MR entero- and colonography. When the DCE-sequence was added to the MR entero- and colonography protocol sensitivity increased to 70% and 74%, specificity was 100% and 80% for observer 1 versus observer 2 (AUC 0.783 and 0.658 respectively).

**Figure 1.** ROC graph depicting the sensitivity and specificity of the different (combinations of) modalities.

Combined MR entero- and colonography and ultrasound had a sensitivity of 70% and 74% and a specificity of 100% and 80% for observer 1 versus observer 2 (AUC 0.850 and 0.770 respectively). When DCE-MRI was used in combination with ultrasound the sensitivity was 83% and 87%, specificity 100 and 80% for observer 1 versus observer 2 (AUC 0.913 and 0.835 respectively). Six patients with a false negative MR entero- and colonography only had relatively mild lesions at endoscopy varying between friability, exudate, granularity, loss of vascular pattern or small aphthae (D’Haens histology score median 10 (range 10-13) (figure 3). Four patients (40%)
also had severe lesions such as ulcerations and cobblestoning (D’Haens histology score median 11 (range 6-11). One patient had additional lesions in the duodenum that could not be assessed on MR entero- and colonography (D’Haens histopathology score 11). In the terminal ileum and colon, the pathology score did not correlate with maximum enhancement or initial slope of increase in IBD patients.

**Figure 2.** 16 year old male patient with Crohn’s disease. At colonoscopy swelling and deep ulceration were seen in the terminal ileum and cecum. MR entero- and colonography and ultrasound both diagnosed Crohn’s disease.

2A+B. Axial and coronal T2w SSFSE image with fat saturation shows thickened bowel wall (6 mm both observers, arrow) with high signal intensity of the terminal ileum indicating edema in the wall.

2C. Axial T1 weighted SPE image shows layered enhancement (arrow).

2D. Ultrasound shows thickened terminal ileum of 3.4 cm.
Figure 3. 16 year old female patient with UC. Mild lesions in ascending colon, transverse colon, descending colon and rectum. Severe lesions in ascending colon. Based on MR entero- and colonography both observers diagnosed no IBD, but IBD was diagnosed with ultrasound.

2E. Endoscopy shows deep ulcerations in the cecum.

3A. Endoscopy shows ulcerations in the ascending colon.

3B. Coronal T2 weighted images shows no apparent thickened bowel wall (<3mm).
Distinguishing Crohn’s disease from ulcerative colitis

Sensitivity for distinguishing CD (table 2) was 50% for ultrasound and 58% (observer 1) and 50% (observer 2) for MR entero- and colonography. Specificity was 87% for ultrasound and 100% (observer 1) and 91% (observer 2) for MR entero- and colonography. Positive predictive value (PPV) was 75% for ultrasound and 100% (observer 1) and 88% (observer 2) for MR entero- and colonography. Negative predictive value (NPV) was 58% for ultrasound, 67% (observer 1) and 65% (observer 2) for MR entero- and colonography. When lesions were present in the terminal ileum at MR enterography, the diagnosis was CD in 100% of cases. On ultrasound, this was 83% (5/6 patients).

Sensitivity for distinguishing UC (table 2) was only 10% for ultrasound and 30% for MR entero- and colonography (both observers). Specificity was 85% for ultrasound, and 85% (observer 1) and 77% (observer 2) for MR entero- and colonography. PPV was only 10% for ultrasound and 30% (both observers) for MR entero- and colonography. NPV was 55% for ultrasound, 61% (observer 1) and 59% (observer 2) for MR entero- and colonography.

3C. Contrast enhanced T1-weighted sequence shows no enhancement of the bowel wall.

3D. Ultrasound of cecum shows normal bowel wall (2mm). On ultrasound diagnosis of Crohn’s disease was made due to dilatation of a small bowel loop (without a visible stenosis), distinguishing Crohn’s disease from ulcerative colitis.
Table 2. Results comparing the findings of magnetic resonance imaging (MRI) and ultrasound (US) versus endoscopy for diagnosing Crohn’s disease and ulcerative colitis

<table>
<thead>
<tr>
<th>Crohn’s disease</th>
<th>Number</th>
<th>Sensitivity 95% CI</th>
<th>Specificity 95% CI</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>US versus endoscopy</td>
<td>11</td>
<td>0.55 (0.28-0.79)</td>
<td>0.78 (0.45-0.94)</td>
<td>0.648</td>
</tr>
<tr>
<td>MRI versus endoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td>12</td>
<td>0.58 (0.32-0.81)</td>
<td>1.00 (0.74-1.00)</td>
<td>0.710</td>
</tr>
<tr>
<td>Observer 2</td>
<td></td>
<td>0.50 (0.25-0.75)</td>
<td>0.91 (0.62-0.98)</td>
<td>0.727</td>
</tr>
<tr>
<td>Colitis ulcerosa</td>
<td>Number</td>
<td>Sensitivity 95% CI</td>
<td>Specificity 95% CI</td>
<td>AUC</td>
</tr>
<tr>
<td>US versus endoscopy</td>
<td>10</td>
<td>0.10 (0.02-0.47)</td>
<td>0.85 (0.58-0.96)</td>
<td>0.534</td>
</tr>
<tr>
<td>MRI versus endoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td>10</td>
<td>0.30 (0.11-0.60)</td>
<td>0.85 (0.58-0.96)</td>
<td>0.534</td>
</tr>
<tr>
<td>Observer 2</td>
<td></td>
<td>0.30 (0.11-0.60)</td>
<td>0.77 (0.50-0.92)</td>
<td>0.551</td>
</tr>
</tbody>
</table>

CI= confidence interval, AUC= area under the ROC curve.

Interobserver variability results for MR entero- and colonography

Kappa value for the presence of IBD was 0.630 between the two MR entero- and colonography observers (moderate agreement). For the diagnosis CD or UC the kappa value was 0.638.

DISCUSSION

Our study shows that ultrasound and/or DCE-MR entero- and colonography cannot replace endoscopy in the diagnostic work-up of children with suspected IBD. Ultrasound and DCE-MR entero- and colonography can be used to diagnose IBD in a pediatric population, but not to exclude IBD. With current up-to-date imaging techniques, it is not possible to distinguish between CD and UC. Our study is the first to compare both ultrasound and DCE-MRI entero- and colonography for detecting IBD and distinguishing between UC and CD. The use of MR colonography and DCE-MRI is new in the pediatric population.

For the diagnosis of IBD, sensitivity was 55% for ultrasound and 57% for MR entero- and colonography. By combining MR entero- and colonography and ultrasound, the sensitivity for detecting IBD increased up to 74%. When adding a DCE-sequence sensitivity increased to a maximum of 87%.

In our study we reached a lower sensitivity for diagnosing IBD both with ultrasound and MR entero- and colonography compared to some other studies (81-100%) (4,5,8). In these studies the patient cohort included also patients with known IBD (4,5). A higher sensitivity can be expected in a cohort with already diagnosed IBD because these patients are more...
likely to show severe inflammation and may have sequelae of previous exacerbations. A study by Casciani et al. reached a sensitivity of 100% for detecting CD comparing MR enterography with a combined reference standard of UGT endoscopy, ileocolonoscopy, histology, laboratory results and clinical investigation (8). Although they also included patients with suspected IBD, their calculated sensitivity is for CD only. The parameters we used in our study were the same MRI features as used in previous studies (4,5,7,8,19,20). The false negative cases in our study could be due to the fact that some were patients (n=3) with UC with only inflammation in the descending colon and rectum which is difficult to detect with ultrasound because of its deep pelvic position and with MRI because adequate distention is not always achieved without the administration of rectal contrast. Furthermore, eight of our false negative cases only had mild disease activity. It is known that mild disease activity (e.g. erythema of bowel wall) is more difficult to detect with MRI compared to severe inflammation (deep ulcerations and cobblestoning) (18). In patients with mild disease activity MRI features such as T1 enhancement and increased bowel wall thickness are sometimes not present, as was the case in this study. Combining DCE-MRI and ultrasound increased the sensitivity for diagnosing IBD up to 87%. However, we do not recommend imaging as a first line technique for the diagnosis of IBD, because an unacceptable number of children with IBD will be missed if endoscopy will not be performed.

MR entero- and colonography and ultrasound could not distinguish CD from UC. Sensitivity ranged from 50 to 58% for MR entero- and colonography and 55% for ultrasound in detecting CD and 30% for MR entero- and colonography in UC and 10% for ultrasound. Current data on imaging techniques to differentiate between CD and ulcerative colitis is scarce as most research focuses on the diagnosis of IBD and not the specific subtypes of IBD. One previous study also found that distinguishing between CD and UC was not possible with MRI (accurate diagnosis in 0%, 14% and 43% of cases depending on the observer) (7). Based on our study results, it is not possible to differentiate between CD and UC except when there are lesions in the terminal ileum. When lesions were present in the terminal ileum at MR enterography, the diagnosis was CD in 100% of cases. This proves that MR enterography is a valuable tool in the diagnostic work-up of children with suspected IBD, especially when the terminal ileum cannot be evaluated during endoscopy.

MR entero- and colonography interobserver variability was moderate both for determining IBD and distinguishing between CD and UC, which is consistent with the results of a previous study (7).
Our study had several strengths. We compared two state-of-the-art imaging techniques with a pathology based reference standard. The ultrasound exam included Doppler measurements and the MRI a diffusion weighted imaging of both small bowel and colon and a DCE-sequence. Bowel preparation was optimal as both the small and the large bowel were distended.

We are aware, however, of the limitations of our study: there was a high prevalence of IBD in our study group. We had anticipated a prevalence of 50% based on previous clinical practice. In our hospital we only perform UGT and ileocolonoscopy under general anesthesia when there is sufficient indication based on patient history, clinical evaluation and laboratory results. In our study cohort there were only five patients that were ultimately not diagnosed with IBD, which diminishes the certainty of our results regarding the specificity. Second, in our study the rectum could not be assessed on ultrasound in all but one patient due to its deep pelvic localization. With DCE-MRI, the size of the dynamic volume was 35 mm in the axial plane. The volume was placed to contain as many bowel segments as possible in the volume but this precluded in practice the rectum because of the posterior location of the rectum. In a retrospective study with 207 patients with IBD, ultrasound and MR entero- and colonography were compared in detecting of lesions on a per patient basis. Missed lesions on ultrasound were mostly due to anatomic location (lower pelvis) or technical problems (bowel gas) and with MR entero- and colonography subtle findings were more difficult to detect (22).

Third, we did not determine the inter-observer variability for ultrasound for logistical reasons. As all patients already underwent one additional ultrasound and additional MRI sequences we determined it to be too burdensome to perform the ultrasound by two observers.

Fourth, our DCE-MRI protocol had high temporal resolution to enable free breathing during the sequence. Because of respiratory motion registration of the DCE-dataset was necessary. We used non-rigid registration with a residual misalignment of 1 to 2 voxels which we considered sufficiently low to justify a ROI-analysis of the segments. Because some of the patients had small antecubital veins, it was not possible to inject the intravenous contrast medium with 5 ml/s in all patients. For the DCE analysis the contrast medium needs to be injected at the highest speed possible. We used the highest speed that was possible based on the size of the intravenous catheter.

In conclusion, DCE-MR entero- and colonography and ultrasound can be used to diagnose IBD in a pediatric population, but not to exclude IBD. Differentiation between CD and UC is not possible with ultrasound and MR entero- and colonography. Therefore, in the diagnostic assessment of children with suspected IBD endoscopy cannot be replaced by these techniques.
REFERENCES


