Crohn’s disease, advances in MRI

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Citation for published version (APA):

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Chapter 6

Accuracy of abdominal ultrasound and MRI for the detection of Crohn’s disease and ulcerative colitis in a paediatric population

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Abstract
Background:
Endoscopy is currently used as primary technique to diagnose IBD in children; its major limitation is the associated burden. The purpose of this study was to assess the accuracy of ultrasound and (DCE-)MRI for diagnosing IBD and for distinguishing between Crohn’s disease and ulcerative colitis.

Methods:
Consecutive consenting paediatric patients with suspected IBD were included. All patients underwent diagnostic work-up including ileocolonoscopy and upper gastrointestinal endoscopy under general anaesthesia, abdominal ultrasound and MR enterocolonography 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 paediatric patients were included (15 males, mean age 14, 10-17 years). Diagnosis was Crohn’s disease in 12 patients (43%), ulcerative colitis 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 enterocolonography, 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 Crohn’s disease and ulcerative colitis when terminal ileum lesions were found.

Conclusions:
Ultrasound and MRI can be used to diagnose IBD in a paediatric population but cannot be used to exclude IBD or to differentiate between Crohn’s disease and ulcerative colitis.

Introduction
IBD comprises two major disorders: ulcerative colitis and Crohn’s disease. 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 paediatric series, the prevalence of indeterminate colitis ranges from 5% to 30%.

In children suspected of IBD, it is important to establish the correct diagnosis because there is a difference in treatment strategies of Crohn’s disease and ulcerative colitis. 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 MRI. In most countries, upper and lower endoscopies in children are performed under general anaesthesia. 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 paediatric population. Lower sensitivity is due to missed cases when they only have mild disease activity such as erythema of the bowel wall. As ultrasound is a non-invasive technique, it is well tolerated by children. Drawback is that deeper situated structures and some anatomic locations such as the upper gastrointestinal tract are more difficult to assess with ultrasound.

MRI is increasingly used for diagnosis and assessing disease activity of the small bowel in children with Crohn’s disease. Sensitivity in paediatric patients for detecting IBD ranges from 61 to 92% and specificity from 60 to 92%. 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 extracellular extravascular space and in that way produces parenchymal enhancement. In inflammatory tissue a marked increase in signal intensity of actively diseased bowel can be seen due to increased vascular permeability and this could possibly be helpful in the diagnosis of IBD.
Chapter 6

The purpose of our study was to assess the accuracy of abdominal ultrasound and MR entero- and colonography for the diagnosis of IBD in comparison to upper and lower tract endoscopy in children. Our second aim was to determine if (DCE-)MR entero- and colonography and abdominal ultrasound can differentiate between Crohn’s disease and ulcerative colitis.

Materials and Methods
Thirty consecutive paediatric 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 paediatric ulcerative colitis activity index (PUCAI) and paediatric Crohn’s disease activity index (PCDAI) were determined for all patients at inclusion.

Reference standard
The reference standard procedure consisted of endoscopic findings and histopathological interpretation. The diagnosis based on UGT endoscopy, ileocolonoscopy and histopathology results was established by two paediatric gastroenterologists in consensus. Endoscopy was performed under general anaesthesia by an expert paediatric endoscopist. 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, coecum and ascending colon, transverse colon, descending colon and sigmoid, 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 oesophagus. If suspect lesions were present, then these were biopsied; otherwise, random tissue sampling was performed. An endoscopic diagnosis was given by the endoscopist (Crohn’s disease, ulcerative colitis, 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. 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 SPE sequence. In the post-contrast 3D T1-weighted fast SPE sequence 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 butylscopalaminebromide (Buscopan, Boehringer, Ingelheim, Germany) were given intravenously, immediately before the DCE-MRI sequence and before the post-contrast 3D T1-weighted SPE sequences.

DCE-MRI image analysis
DCE-MRI registers changes in signal intensity over time during the administration of intravenous contrast medium. To calculate the difference in signal intensity, ROIs were drawn with ITK-SNAP 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

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volume 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. 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 paediatric 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 oedema, 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 Crohn’s disease and ulcerative colitis, the localization of lesions was indicative in distinction to proximal were indicative of ulcerative colitis; skip lesions and transmural inflammation were indicative of Crohn’s disease. As in MRI, the localization of lesions was indicative in distinguishing between Crohn’s disease and ulcerative colitis.

Abdominal ultrasound
Bowel wall ultrasound examinations were performed by observer 2 or one other paediatric 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 ulcerative colitis; skip lesions and transmural inflammation were indicative of Crohn’s disease. As in MRI, the localization of lesions was indicative in distinguishing between Crohn’s disease and ulcerative colitis.

Power analysis
We anticipated a sensitivity for diagnosing IBD of 81.8% and 95% confidence intervals of 0.42%. 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 ulcerative colitis and Crohn’s disease.

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 Crohn’s disease, 10 ulcerative colitis, one indeterminate colitis. Five patients did not have IBD (18%). We excluded the patient with indeterminate colitis from the subgroup analysis (distinguishing Crohn’s disease versus ulcerative colitis) because the subgroup indeterminate colitis would have been too small (N=1). This patient was however included in the IBD analysis.

In patients with Crohn’s disease median PCDAI score was 31 (IQR 20-39), in patients with ulcerative colitis median PUCAI score was 43 (IQR 29-79). Median time between endoscopy and ultrasound/MR entero- 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 entero- 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 Crohn’s disease, three ulcerative colitis) and no IBD in 13 patients. With MR entero- and colonography, diagnosis was IBD in 13 patients (eight Crohn’s disease, five ulcerative colitis) and no IBD in nine patients.

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, 0.783 for observer 1 MR entero- and colonography and 0.658 for observer 2. When the DCE-sequence was added to the MR entero- and colonography protocol sensitivity increased to 70% and 74%, specificity was 100% and 80% (AUC 0.783 and 0.658 respectively, for observer 1 versus 2).

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 was 0.850 for observer 1 and 0.770 for observer 2. When DCE-MRI was used in combination with ultrasound the sensitivity was 83% and 87%, specificity 100 and 80% (observer 1 versus 2) (AUC 0.913 for observer 1, 0.835 for observer 2). Six patients with a false negative MR entero- and colonography only had relatively mild lesions at endoscopy varying between friability, edema, granularity, loss of vascular pattern or small aphtae (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 enter- and colonography (D’Haens histopathology score 11).

In the terminal ileum, the pathology score did not correlate with maximum enhancement or initial slope of increase in IBD patients. Mean colonic histopathology scores were not different between ulcerative colitis and Crohn’s disease patients but were significantly higher than in control patients (3 versus 6, p=0.047).

**Distinguishing Crohn’s disease from ulcerative colitis.**

In IBD patients ultrasound had a sensitivity of 55% for detecting Crohn’s disease (figure 4) and MR enter- and colonography 50% (observer 2) and 58% (observer 1), respectively. Specificity was 78% for ultrasound and 91 (observer 2) and 100% (observer 1) for MR enter- and colonography. PPV was 75% for ultrasound, 88% (observer 1) and 100% (observer 2) for MR entero- and colonography. NPV was 58% for ultrasound, 67% (observer 1) and 65% (observer 2) for MR entero- and colonography. AUC was 0.648 for ultrasound, 0.710 for observer 1 and 0.727 for observer 2. When lesions were present in the terminal ileum at MR entero- and colonography, the diagnosis was Crohn’s disease in 100% of cases. On ultrasound, this was 83% (5/6 patients).

Sensitivity for distinguishing ulcerative colitis was only 10% for ultrasound and 30% for MR enter- and colonography (both observers). Specificity was 85% for ultrasound, and 85% (observer 1) and 77% (observer 2) for MR entero- and colonography (figure 5). 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. AUC was 0.534 for both ultrasound and MRI observer 1, and 0.551 for observer 2.

**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 Crohn’s disease or ulcerative colitis the kappa value was 0.638.

**Discussion**

Our study shows that ultrasound and MR entero- and colonography can be used to diagnose IBD in a paediatric population, but not to exclude IBD. With current up-to-date imaging techniques, it is not possible to distinguish between Crohn’s disease and ulcerative colitis. Our study is the first to compare both ultrasound and MRI entero- and colonography for detecting IBD and distinguishing between ulcerative colitis and Crohn’s disease.

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 other studies (81-100%)\(^4,5,7,8,19,20\). In these studies the patient cohort included also patients known with 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 sequels of previous exacerbations. A study by Casciani et al reached a sensitivity of 100% for detecting Crohn’s disease using a combined reference standard of UGT endoscopy, ileocolonoscopy, histology, laboratory results and clinical investigation\(^1\). Although they also included patients with suspected IBD, their calculated sensitivity is for Crohn’s disease only. The lower sensitivity in our study could be due to the fact that some of our false negative cases (three patients) were patients with ulcerative colitis 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 distension 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)\(^5\). 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. The difference in sensitivity cannot be explained by the parameters used in our study, because we assessed the same MRI features as previous studies\(^5,7,8,19,20\) used such as thickened bowel wall, increased mural T2 signal intensity, T1 bowel wall enhancement, layered enhancement, absence of hastrations, presence of peri-colonic mesenteric oedema, comb sign, creeping fat and bowel dilatation and diffusion restriction on the DWI sequence to detect all possible inflammatory changes in our patient cohort. We tried to define all MRI...
parameters according to precise criteria but some features such as T1 enhancement and T2 signal intensity were evaluated in a subjective manner, because measurements are not more accurate than subjective assessment.

Although combining DCE-MRI and ultrasound increases the sensitivity up to 87% 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 Crohn’s disease from ulcerative colitis. Sensitivity ranged from 50 to 58% for MR entero- and colonography and 55% for ultrasound in detecting Crohn’s disease and 30% for MR entero- and colonography in ulcerative colitis and 10% for ultrasound.

Current data on imaging techniques to differentiate between Crohn’s disease 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 Crohn’s disease and ulcerative colitis was not possible with MRI (accurate diagnosis in 0%, 14% and 43% of cases depending on the observer). Based on our study results, it is not possible to differentiate between Crohn’s disease and ulcerative colitis except when there are lesions in the terminal ileum.

MR entero- and colonography interobserver variability was moderate both for determining IBD and distinguishing between Crohn’s disease and ulcerative colitis, which is consistent with the results of a previous study.

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 anaesthesia 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.

In our study the rectum could not be assessed on ultrasound in all but one patient due to its deep pelvic localization. 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. 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.

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, MR entero- and colonography can be used to diagnose IBD in a paediatric population, but not to exclude IBD. Differentiation between Crohn’s disease and ulcerative colitis 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.

Acknowledgement
The authors would like to acknowledge Eline Deurloo, MD for performing some of the ultrasound exams.
References


