



Is MR Enterography in Addition to Ileocolonoscopy Necessary in All Newly Diagnosed Adults with Crohn's disease?

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Abstract

Background: The value of Magnetic Resonance Enterography (MRE) in determining the extent and severity of Crohn's Disease (CD) in addition to a complete ileocolonoscopy at the time of the primary diagnosis has been advocated in recent guidelines though not yet been studied. The aim of this study was to assess the additional value of MRE following initial diagnostic ileocolonoscopy of CD.

Methods: Patients who underwent MRE within 3 months of primary ileocolonoscopy were retrospectively included in the analysis. Additional findings on MRE next to ileocolonoscopy were assessed including strictures, entero-enteral fistula, abscesses and extended small bowel disease activity. MRE findings were subsequently analyzed in different CD phenotypes.

Results: A total of 163 newly diagnosed CD patients were included in the analysis. MRE revealed additional findings in 28% (45/163) of all patients. Prevalence of additional MRE findings was 67% (21/32) in those cases in which ileum could not be intubated, compared to 18% (24/131) in patients with a complete ileocolonoscopy. In patients without ileitis at ileocolonoscopy no additional lesions were seen on MRE. Strictures, entero-enteral fistula and abscesses were mostly observed during MRE examination in patients with severely active ileitis at endoscopy.

Conclusions: Prevalence of MRE findings next to ileocolonoscopy in newly diagnosed CD patients is high in endoscopically assessed stricturing disease and severe disease activity of the terminal ileum, corroborating the use of standard diagnostic MRE in these clinical circumstances.

Keywords: CD; Crohn's disease; IBD, Inflammatory Bowel Disease; MRE, Magnetic Resonance Enterography

Introduction

Crohn's Disease (CD) is a chronic transmural inflammatory disease of the gastro-intestinal tract, which widely varies in presentation, extent and location. A single gold standard for the diagnosis of CD is not available but is confirmed by clinical evaluation and a combination of endoscopic, histological,

radiological, biochemical investigations and occasionally surgery. For diagnostically assumed CD, ileocolonoscopy with biopsies is a well-established first line procedure to confirm the diagnosis [1]. Disease localization at primary diagnosis is reported in 33% of patients to be limited to the terminal ileum, in 47% of the patients limited to the colon and in 20% ileocolonic lesions have been reported [2].

Current diagnostic guidelines recommend additional routine small bowel imaging in all newly diagnosed CD patients,

irrespective of the findings at ileocolonoscopy. However, this recommendation is solely based on the expert opinion of a panel, as studies on this matter are lacking [3]. Magnetic Resonance Enterography (MRE) is the recommended radiological technique for determining the extent and complications of CD, considering its diagnostic accuracy, lack of ionizing radiation and patient acceptance compared to Ultrasound, Computed Tomography Enterography and Magnetic Resonance Enteroclysis [3-16]. MRE has a high sensitivity in the assessment of terminal ileum disease activity, fistulas, strictures, and abscesses as well as the extent of small bowel activity [17-18].

However, the complementary value of MRE in addition to ileocolonoscopy in newly diagnosed CD patients remains yet unclear, as it has not yet been studied. In patients with a non-complicated CD in the colon and/or terminal ileum, small bowel imaging is suspected to provide little extra information compared to ileocolonoscopy alone, especially in isolated colonic disease [19]. On the other hand, an additional MRE could provide vital information in more elaborate and penetrating forms of small bowel CD, such as the detection of strictures, extended small bowel activity, fistulas or abscesses. Therefore, the aim of this study was to assess the value of MRE regarding new clinical relevant findings in addition to ileocolonoscopy at primary diagnosis of CD. Moreover, we wanted to identify CD patients that would benefit the most from an additional MRE at the time of primary diagnosis.

Methods

Study Population and Period

All patients labeled with the Diagnosis Treatment Combination (DTC) code for CD, including ambulatory setting and hospital admissions at a large regional hospital in Arnhem, The Netherlands (Rijnstate Hospital) between 2009 and 2015 were retrospectively reviewed (Figure 1). The primary CD diagnosis was established and registered by the treating physician and was based on a combination of endoscopic, histological, radiological and/or biochemical investigations according to the Lennard-Jones criteria. Patients of 16 years and older, who underwent a MRE following ileocolonoscopy at primary diagnosis, within a period of 3 months, were included. Patients primarily diagnosed before 2009 were not included due to possible changes in MRE protocol.

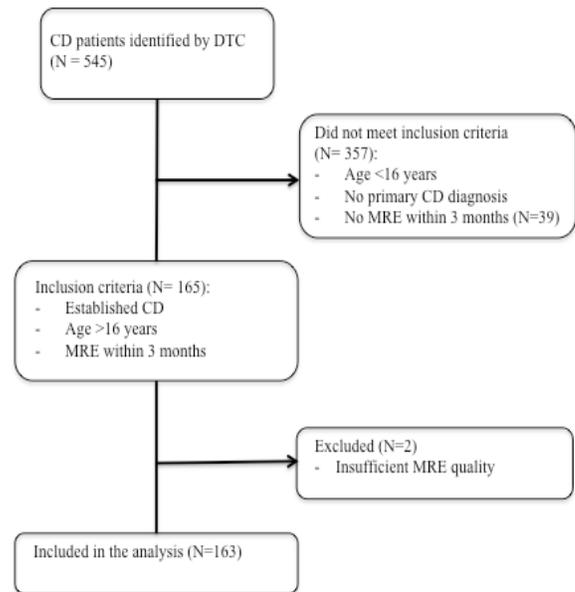


Figure 1: Inclusion diagram of the patients.

Patients with a diagnosis of Ulcerative Colitis (UC), Inflammatory Bowel Disease Unclassified (IBD-U) or an otherwise doubtful CD diagnosis, and in case of inadequate MRE quality were excluded from the analysis. From the medical records of the included patients the following data were retrieved: patient age, gender, date and findings of ileocolonoscopy at the time of primary diagnosis, date and findings of MRE, time to follow-up, disease location and behavior at the time of primary diagnosis according to the Montreal classification. Subgroups were made based on Montreal classifications, intubation of terminal ileum during endoscopy (yes or no) and severity of the ileitis (mild or severe). The cause for not intubating the ileum was identified and these patients were analyzed separately.

The Montreal classification was used to classify CD location [ileal (L1), colonic (L2), ileocolonic (L3)] and disease behavior [non-stricturing, non-penetrating (B1), stricturing (B2), and penetrating (B3)] based on primary ileocolonoscopy [20, 21]. Gastroesophageal involvement was not considered in this study as not all patients underwent upper endoscopy. Subjects with both stricturing and penetrating disease were classified as having

penetrating disease (B3). Perianal fistulizing disease was recorded as a separate modifier (+P) and this localization did not constitute penetrating disease (B3) on its own.

Ileocolonoscopy

Patients underwent endoscopy under conscious sedation. The ileocolonoscopy was performed after standard bowel preparation with 4 liter of polyethylene glycol electrolyte solution. The ileocolonoscopy was scored for presence of ileitis and/or colitis, severity of inflammation in the terminal ileum, stenosis and fistulas based on the report made by the performing endoscopist. Severity of inflammation in the terminal ileum was either classified as mild or severe, while colitis was only noted as present or absent. The ileitis was scored as mild in the presence of small aphthous ulcers (estimated diameter 0.1-0.5 centimeters) separated by normal mucosa and as severe when large ulcers (estimated diameter >0.5 centimeters) and/or diffuse inflamed mucosa was seen. Stenosis was defined, as a localized narrowing of the intestinal lumen reported by the endoscopist, either passable or not passable with the scope.

Magnetic Resonance Enterography

MRE was performed according to the standard local protocol. Patients fasted for at least 4 hours and were asked to drink 1.0 liter of a water-based oral preparation fluid containing 2,5% mannitol and 0,5% locust bean gum, in a time span of 45 minutes before the MRI, without any particular preparation of the colon. MRI scans were performed with the patient in prone position, using a body coil on a 1.5T MRI unit (Intera 1.5 T, Philips medical systems, Best, Holland). Patients were given butylscopolamine 20 mg intravenously, as intestinal motility inhibitor immediately before the examination to avoid bowel peristalsis artifacts. Patients were scanned in the prone position to avoid wall movement of the abdomen.

The scanning protocol included a coronal breath-hold T2-weighted Single-Shot (SSh) turbo spin-echo and a coronal T2 breath-hold balanced Fast Field Echo (FFE). The field of view of these T2 weighted studies was the whole abdomen, from the xyphoid process to the pubic bone. Slice thickness was 5 mm consecutive, which resulted in an average of 30 images in the coronal plane. After 60 seconds of manual administration of the intravenous contrast medium (Gadoteric acid, Dotarem) (0.5 mmol/ml) 0.2 ml per kg body weight, T1 weighted sequences were applied in the transverse and coronal plane with a fat saturation Spectrally Attenuated Inversion Recovery (SPAIR).

The MRE report was scored for the presence of findings such as terminal ileitis (terminal ileum affected adjacent to the ileocecal valve), preterminal ileitis (more than 10 cm normal ileum between the ileocecal valve and the affected ileum), extended ileitis (more than 40cm of small bowel affected), stenosis, fistulas and abscesses.

Stenosis was defined as a narrowing of a thickened bowel segment with a proximal area of dilation. Fistulae were defined as tubular tracts with or without high signal intensity, between two small bowel loops. Abscesses were described as a fluid collection, with or without associated air and a well-defined wall. Mural contrast enhancement was considered present if there was a clear visual enhancement of a small bowel segment compared to adjacent loops of the terminal ileum, at visual assessment. All these scans were re-examined by an experienced abdominal radiologist who was blinded to the patient data.

Outcome Measures

Primary outcome measures were the percentage of patients with additional small bowel findings on MRE and the descriptive characteristics of these findings. The findings of ileocolonoscopy and MRE were analyzed and compared between different subgroups: intubation of the terminal ileum during endoscopy (yes or no), different Montreal classification after primary ileocolonoscopy and endoscopic severity of the ileitis (mild or severe).

Statistical Analysis

Statistical analysis of the data was performed using IBM SPSS statistics (SPSS 21.0). Categorical variables were described using frequencies and percentages. Continuous variables were summarized using medians and range. The Pearson's chi-squared or Fisher-Exact test was used to determine statistical significance between proportions. P values less than 0.05 were considered to indicate statistical significance.

Ethical Considerations

Approval of the local ethics and feasibility committee for medical research from the Rijnstate hospital Arnhem, in The Netherlands was obtained in August 2015. The study was performed according to the principles of the Declaration of Helsinki. Furthermore, there was no conflict of interest or sponsoring involved.

Results

The study population consisted of 163 patients with CD who underwent MRE within 3 months of primary diagnosis by ileocolonoscopy. The main baseline characteristics and endoscopic findings of our patients are summarized in (Tables 1 and 2). Two CD patients were excluded because the MRE quality was insufficient to examine the ileum due to lack of sufficient distension of the small bowel. A number of 39 newly diagnosed CD patients did not undergo MRE within 3 months of initial ileocolonoscopy and were therefore excluded from the analysis (Figure 1). Out of these patients, 10 (26%) had colonic CD with normal ileum on ileocolonoscopy, 16 (41%) had mild ileitis on ileocolonoscopy, 12 (30%) had severe ileitis and 1 patient had an incomplete

ileocolonoscopy because of stricture. The patient with incomplete colonoscopy and 2 other patients with severe disease underwent a CT of the abdomen next to ileocolonoscopy.

Baseline characteristics	Number of patients	Median (spread)/ Percentage
Age at diagnosis	163	28 years [16-72]
→ A2 (16-39 years)	116	71.2%
→ A3 (>40 years)	47	28.8%
Male	61	37.4%
Female	102	62.6%
Perianal disease (+p)	23	14.1%
Days between MRE and ileocolonoscopy	163	11 days [0-92]
< 1 week	64	39.3%
1 week - 1 month	70	42.9%
1 month - 3 months	29	17.8%

Table 1: Baseline characteristics of patients at presentation.

Ileocolonoscopy characteristics	Number of patients (%)
Procedure (N=163)	
Ileum intubated	131(80.4%)
Ileum not intubated	32 (19.6%)
→ due to technical limitations	5 (3.1%)
→ due to stenosis	27 (16.5%)
Location of stenosis	
→ colon	7 (4.3%)
→ ileocecal valve	20 (12.3%)
Ileum inflammation severity (N=131)	
→ no active inflammation	20 (15.3%)
→ mild	48 (36.6%)
→ severe	63 (48.1%)
Localization at endoscopy (N=131)	
→ isolated ileum activity (L1)	66 (50.4%)
→ isolated colonic activity (L2)	17 (13.0%)
→ ileocolonic activity (L3)	48 (36.6%)

Behavior at endoscopy (N=131)	
Non-stricturing/Non-penetrating (B1)	100 (76.3%)
Stricturing (B2)	29 (22.1%)
→ passable with scope	15 (11.5%)
colon	1 (0.8%)
ileocecal valve	5 (3.8%)
ileum	9 (6.9%)
→ impassable with scope	14 (10.7%)
ileum	
Entero-enteral fistulas (B3)	2 (1.5%)

Table 2: Findings at ileocolonoscopy in all patients.

Endoscopic Findings

A total of 131/163 (80%) patients had successful endoscopic intubation of the terminal ileum during endoscopy. In 32/163 (20%) patients the terminal ileum was not intubated due to stenosis (16.5%) or technical limitations (3.1%) The findings of ileocolonoscopy, including disease location and endoscopic severity are described in table 2. From the 20 patients with no endoscopic signs of active ileal inflammation, 17 patients had isolated colonic CD with a normal endoscopic and histologic aspect of the terminal ileum. In three patients ileal disease was present in the form of fibrotic scars, post-inflammatory polyps and stricturing of the terminal ileum without signs of active inflammation at the time of the primary ileocolonoscopy.

Magnetic Resonance Enterography findings

The Magnetic Resonance Enterography findings in addition to ileocolonoscopy findings are summarized in (Table 3). In 28% of all patient's additional small bowel lesions were found on MRE after ileocolonoscopy. Additional findings on MRE were present in 18% of the patients following complete ileocolonoscopy compared to 66% of the patients without ileum intubation (p<0.05) (Table 3).

No statistically significant difference was found between patients with isolated ileum (L1) and ileocolonic (L3) endoscopic disease. Patients with isolated colonic disease during ileocolonoscopy (L2) showed no additional small bowel findings on MRE, precluding Chi-square testing in this group. Patients with endoscopic stricturing disease (B2) had more new lesions on MRE compared to non-stricturing/non-penetrating disease (B1) (p<0.05). In the patients with signs of entero-enteral fistula on primary endoscopy (B3), the MRE confirmed the presence of fistula and revealed new lesions such as stenosis or abscess (Table 3). The additional MRE findings in mildly active endoscopic ileitis

were restricted to five cases showing ileitis in the proximal ileum (skip lesions) without small bowel complications and one case of extended ileitis (>40 cm).

Magnetic Resonance Enterography findings	Additional findings (%)	New terminal ileitis (%)	Preterminal ileum activity (%)	Length >40cm (%)	New stenosis (%)	New entero-enteral fistula (%)	Abscesses (%)	Change in Montreal classification (Behavior/Location)
All patients (N=163)	45 (27.6%)	21 (12.9%)	16 (9.8%)	6 (3.7%)	3 (1.8%)	9 (5.5%)	6 (3.7%)	11 (6.7%)/14 (8.5%)
Ileum intubated (n= 131)	24 (18.3%)*	1 (0.8%)	12 (9.2%)	5 (3.8%)	3 (2.3%)	7 (5.3%)	5 (3.8%)	8 (6.1%)/0 (0.0%)
Ileum not intubated (n=32)	21 (65.6%)*	20 (62.5%)	4 (12.5%)	1 (3.1%)	0 (0%)	2 (6.3%)	1 (3.1%)	3 (9.4%)/13 (40.6%)
Clinical phenotype after ileocolonoscopy (N=131)								
Ileal (L1) (n=66)	14 (21.2%)**	0 (0.0%)	6 (9.1%)	3 (4.5%)	2 (3.0%)	5 (7.6%)	2 (3.0%)	5 (7.5%)/0 (0.0%)
Colonic (L2) (n=17)	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)/0 (0.0%)
Ileocolonic (L3) (n=48)	10 (20.8%)**	1 (2.1%)	6 (12.5%)	2 (4.2%)	1 (2.1)	2 (4.2%)	3 (6.3%)	3 (6.3%)/0 (0.0%)
Ileum inflammation severity (N= 114)								
Non-stricturing/non-penetrating (B1) (n=100)	12 (12.0%)*	0 (0.0%)	8 (8 %)	3 (3.0%)	0 (0.0%)	1 (1.0%)	2 (2.0%)	2 (2.0%)/0 (0.0%)
Stricturing (B2) (n=29)	10 (34.5%)*	0 (0.0%)	3 (10.3%)	1 (3.4%)	2 (6.9%)	4 (13.8%)	2 (6.9%)	6 (20.7%)/0 (0.0%)
Penetrating (B3) (n=2)	2 (100%)	1 (50.0%)	1 (50.0%)	1(50.0%)	1 (50.0%)	2 (100%)	1 (50.0%)	0 (0%)/0 (0.0%)
Fibrotic lesions and stenosis without active inflammation (N=3)								
Mild (N=48)	6 (12.5%)	0 (0.0%)	5 (10.4%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)/0 (0.0%)
Severe (N=63)	15 (23.8%)	0 (0.0%)	6 (9.5%)	2 (3.2%)	0 (0.0%)	6 (9.5%)	4 (6.3%)	8 (12.7%)/0 (0.0%)

* p < 0.05; ** p = 0.112

Table 3: Additional findings at MRE next to ileocolonoscopy.

Discussion

In the present study, additional findings on MRE following primary ileocolonoscopy were observed in 28% of newly diagnosed CD patients. The highest percentage of additional MRE small bowel lesions was found in patients with incomplete ileocolonoscopy (67%) and in patients with stricturing endoscopic disease (35%). In isolated colon CD at ileocolonoscopy no additional findings were seen on the MRE. Patients with mild endoscopic ileitis had no small bowel complications on MRE.

Current guidelines recommend additional imaging of the small bowel in all newly diagnosed CD patients, irrespective of the findings at ileocolonoscopy. The underlying reason for this recommendation may be that sensitivity of ileocolonoscopy in determining the location and extent of disease activity, especially in penetrating and stricturing forms of small bowel CD is limited [3]. However, a majority of the patients experience no CD complications at time of first presentation. Previous studies have shown that MRE has a high sensitivity for both assessing the terminal ileum disease activity, fistulas, strictures, and abscesses

as well as the extent of small bowel activity of Crohn's disease [17, 18]. In most studies the accuracy of MRE has been compared with ileocolonoscopy but the complementary diagnostic value of MRE was disregarded [22, 23]. It has recently been stated that nearly half of the Inflammatory Bowel Disease guideline recommendations are based on expert opinion or lack any solid scientific evidence necessitating corroborating (or denying) investigations [24].

In a previous subgroup analysis of the value of MRE next to primary ileocolonoscopy in 49 patients was stated that small bowel imaging provides little extra information in non-complicated CD [19]. Moreover, it was suggested that in isolated colon CD during complete ileocolonoscopy, small bowel imaging adds no information to endoscopy. An important role for MRE was mentioned in case of incomplete ileocolonoscopy or suspicion of complicated disease. However predictive factors of complicated disease were not addressed [19]. Predictive factors for complicated CD might include extensive small bowel disease, young age at diagnosis, perianal disease activity, early stricturing/penetrating disease and smoking but the clinical value of these factors has not

yet been prospectively studied in a large patient cohort [25,26].

One of the strengths of the present study lies in refining the indication for additional small bowel imaging based on macroscopically findings of the primary ileocolonoscopy. Furthermore, the period between the primary ileocolonoscopy and MRE was short, as 82.2% underwent MRE within a month, with an overall a median period of 11 days. Moreover, the number of patients included was sufficiently high to draw robust conclusions. The main limitation of this study was the retrospective design. The prognostic value and clinical impact of the additional MRE findings at the time of the primary diagnosis could not be reliably determined in this study. Furthermore, the inclusion criteria might have induced a selection bias, because only patients who underwent MRE were included. The isolated colonic disease group could therefore be underrepresented in our study.

Assessment of disease extension and activity in patients with CD is required in order to determine the therapeutic strategy, and may have major prognostic implications [27]. The extent of the prognostic impact of small bowel imaging after initial ileocolonoscopy is unclear as a combined disease severity index capturing different prognostic factors, such as clinical phenotype, mucosal lesions and bowel damage, is missing [25,28]. Ileocolonoscopy with biopsies is needed in all suspected IBD cases in order to confirm the diagnosis. However, imaging of the small bowel by MRE in addition to the initial ileocolonoscopy is a costly procedure and the indication should be appropriately argued based on the disease characteristics. Our results confirmed that in case of an incomplete primary ileocolonoscopy, MRE might reveal important new findings regarding small bowel extent and complications of CD. High prevalence of additional findings was also present in case of stricturing of the terminal ileum during a complete ileocolonoscopy. MRE findings in case of mildly active endoscopic ileitis were of limited clinical value and no small bowel complications were seen in this group of patients.

In conclusion, MRE is a valuable addition to ileocolonoscopy in determining the location and extent of CD, in some well-defined groups of newly diagnosed patients. Additional MRE is indicated in all cases of incomplete endoscopy, stricturing and severely active ileitis at primary endoscopy. Furthermore, MRE should also be performed in all cases of endoscopic suspicion of entero-enteral fistula in order to assess the extent of the lesions and presence of concomitant complications such as stenosis and abscesses. In cases of mildly active endoscopic ileitis the additional value of MRE following complete primary ileocolonoscopy was limited and therefore MRE is not routinely indicated in these patients. Moreover, when the disease activity is isolated to the colon during a complete ileocolonoscopy, MRE could be omitted from the diagnostic work-up.

Conflict of Interests: None.

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