Ultra–high-field Magnetic Resonance Enterography in the Diagnosis of Ileitis (Neo-)Terminalis

A Prospective Study

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Background and Goals: Magnetic resonance (MR) enterography provides the advantages of conventional enteroclysis and those of cross-sectional imaging. Adequate luminal distension, combined with ultrafast sequences, results in excellent delineation of mural and extramural manifestations of Crohn’s disease. Recent technical advances, including ultra–high-field strength MR with its capability to provide fast multiplanar images with excellent soft tissue contrast, are only rarely included in abdominal studies.

Study: One hundred four consecutive patients with a proved or suspected diagnosis of ileitis terminalis were prospectively selected for MR imaging studies and ileocolonoscopy. The final diagnosis was based on histopathological findings or based on a combined endpoint of clinical, laboratory, endoscopic, and imaging findings.

Results: According to the endoscopic examination, stenosis was present in 26 patients (25%) and could be ruled out in 78 patients (75%). Total agreement between MR and endoscopy could be reached in 74 patients (71%). Histology indicated absence of inflammation in 50 patients (48%). MR and endoscopic findings were concordant in 38 patients (76%) and 37 patients (74%), respectively. Corresponding results by ileocolonoscopy were 37 true negative, 29 true positive, 4 false positive, and 12 false negative (sensitivity, 70.7%; specificity, 74%).

Conclusions: MR enterography with a 3.0-T scanner is a powerful tool in the evaluation of ileal diseases, and has therefore made MR enterography the first-line modality at our institution in patients with suspected inflammatory bowel disease.

Key Words: 3.0 T magnetic resonance enterography, Crohn’s disease

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Crohn’s disease (CD) is an inflammatory disease with increasing incidence since the 1980s. The ileocolic region is most commonly affected, although any part of the gastrointestinal tract is at risk. The small bowel has been a challenging region to evaluate by imaging. Therefore, there is an ongoing debate about which imaging modality is best for patients with inflammatory bowel diseases (IBDs). Traditionally, ileocolonoscopy with tissue sampling is considered to be the most valuable endoscopic tool for diagnosis and follow-up of disease in the terminal ileum. The advent of video capsule endoscopy and balloon endoscopy has increased diagnostic possibilities. However, the transmural and extramural extent of inflammation cannot be visualized with any of these endoscopic techniques. For years, the gold standard examination for the small bowel has been small bowel barium examination, either by using an enteroclysis technique or by using a small bowel follow-through. Small bowel barium examination is invasive and burdensome, and it is limited by required ionizing radiation. Currently, ultrasonography and computed tomography are often used for the evaluation of the abdomen. Ultrasonography has high sensitivity in diagnosing IBD, particularly of the terminal ileum. Comparative studies of computed tomography enterography have also reported high sensitivities in IBDs. Computed tomography of the abdomen is associated with high-radiation dosages, however, which is worrying because young patients with CD may undergo several such examinations during their lifetime.

Magnetic resonance (MR) enterography has the potential to overcome these limitations and provides the advantages of conventional enteroclysis and those of cross-sectional imaging. Adequate luminal distension, combined with ultrafast sequences, results in excellent delineation of mural and extramural manifestations of CD. Although several MR characteristics of the bowel have been described, most studies lack high patient numbers or validation of the results in an independent cohort with low-disease prevalence. Furthermore, recent technical advances, including ultra–high-field strength MR with its capability to provide fast multiplanar images with excellent soft tissue contrast, are only rarely included in abdominal studies.

The aim of this study was to characterize the accuracy of ultra–high-field MR enterography of the terminal ileum in patients with suspected ileitis (neo-) terminalis at a tertiary referral center. Results were correlated with endoscopic findings and histology.

PATIENTS AND METHODS

Patients included in this single center study were recruited in the IBD outpatient Department of the Gastroenterology Division, a tertiary referral center for gastrointestinal diseases, between April 2007 and March 2008. One hundred four consecutive patients with a proved or suspected diagnosis of ileitis terminalis were prospectively selected for MR imaging studies during a periodic clinical and diagnostic assessment that included a review of each patient’s medical history, a physical examination, blood testing, and an abdominal ultrasound.
Inclusion criteria were clinical symptoms (ie, abdominal pain, diarrhea) and/or laboratory parameters (elevated C-reactive protein, elevated white blood cell count) in patients with confirmed or suspected CD or in patients with histologically verified CD, who had been treated by ileocolic resection. The time interval between operation and study inclusion was at least 6 months. Exclusion criteria included age <18 years, pregnancy, implanted electromedical devices (ie, pacemaker, defibrillator, or spinal electrodes), ferromagnetic cardiac valve prostheses, and ferromagnetic aneurysm clips. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Informed written consent was obtained from all patients in accordance with our institutional quality assurance guidelines. Patients underwent conventional ileocolonoscopy and MR examination within 7 days, and medication for CD had to be stable between both investigations.

Endoscopy Methods

After bowel cleansing on the evening before examination, endoscopy was performed on all patients as a standardized routine procedure under anesthesia with midazolam, ketamine, and propofol using a CF160 AL or PCF 160 AL endoscope (Olympus Deutschland GmbH, Hamburg, Germany). At least 3 biopsies were taken with forceps, transferred to a formaldehyde solution, and sent to the Institute of Pathology for further processing and evaluation. Routine histology was performed on these specimens stained with hematoxylin and eosin. Disease activity was assessed according to the simple endoscopic score for CD. The endoscopic findings in both the terminal ileum and anastomosis (if a patient had previously undergone surgery) were recorded. The anastomosis was defined as part of the terminal ileum for the purposes of comparison with MR enterography results. As some endoscopic and histologic findings are nonspecific for CD, and because these findings are evaluated together in conjunction with clinical presentation and results of patient examination in rendering a final diagnosis of CD, a panel of 2 gastroenterologists (H.E.A. and U.R.), who had 9 and 13 years, respectively, of subspecialty clinical experience in our IBD clinic, was consulted. They constructed 4 reference panels and the ileoscopy and biopsy findings. If biopsy was not performed, the diagnosis was based on the endoscopic findings alone. The presence of CD was considered definite if ileoscopy revealed erosions and/or ulcerations or stenosis, or if abnormal ileoscopic results were combined with the finding of chronic ileitis at biopsy.

Image Assessment

As a blinded branch of the study, the MR investigators who had MR enterography experience of >5 years each, were unaware of the endoscopic procedure but had access to pertinent clinical information for each case as indicated on the imaging requisites forms from referring clinicians (ie, history, abnormal clinical and laboratory findings, and rationale for imaging). MR was performed within 7 days before or after endoscopy. The endoscopist knew that the indication for the procedure was (suspected) CD but did not necessarily know the results of MR enterography.

MR Enterography Procedure

Patients were required to drink a total volume of 1500 to 2000 mL of oral contrast over a course of 60 minutes just before imaging. The oral contrast is a mixture of 50 mg mannitol and 2000 mL water; it is given to distend the bowel. At full and homogeneous distension of all small bowel segments, spasmolytic agents (hyosin-N-butylbromide, eg, Buscopan; 40 mg, Boehringer Ingelheim, Germany) were applied intravenously to suppress small bowel motility and to maintain optimal small bowel distension during the entire scanning time.

The standard imaging protocol included T_{2}-weighted single-shot turbo spin echo (TSE) sequences in coronal orientation with and without fat suppression, and T_{1}-weighted gradient echo sequences after intravenous application of Omniscan (gadodiamide) injection, a formulation of the gadolinium complex of diethylenetriamine penta-acetic acid bismethylamide or dotarem, a gadolinium-containing contrast agent. The following items were studied in the terminal ileum: bowel wall thickness, length of the inflamed segment, presence of mucosal ulceration or mural edema, measurement of wall signal intensity before and after contrast media, evaluation of enlarged mesenteric lymph nodes, and abscesses or fistulae.

All examinations were performed using a 3.0-T MR unit (Achieva, Philips, NL-Best). Patients were placed in supine position in the MR imager. A combination of 2 surface coils was used for signal reception to allow coverage of the entire abdominal area. Total scan time ranged from 30 to 40 min.

Statistical Analysis

The results of MR and endoscopy were correlated with the final diagnosis based on histopathological findings or based on a combined endpoint of clinical, laboratory, endoscopic, and imaging findings. Particularly, in the absence of confirmatory (ie, specific) histology in suspected CD, a positive diagnosis was based on symptoms and on clinical and imaging findings.

Statistical analysis of MR enterography and endoscopic findings for the terminal ileum were performed on a patient level. The sensitivity and specificity of these modalities were determined separately and then in conjunction with regard to the final diagnosis. Results were compared using the
Bowker test. This is an extension of the McNemar test to a $K \times K$ situation. There are now $K$ response categories for the 2 dependent samples. The null hypothesis is that the probabilities in the square table satisfy symmetry or that there is no significant shift from 1 response category to another from sample 1 to sample 2. When the null hypothesis of symmetry is true, then B will have a $\chi^2$ distribution with $K(K-1)$ degrees of freedom. This is the basis of the proposed test by Bowker (1948). If $K = 2$, then B simplifies to the McNemar test statistic. The $\alpha$ level for statistical significance was set at 0.05.

RESULTS

During the study period, 104 consecutive patients (43 of them men) with a mean age of 39.8 years (range, 18 to 68 y) were included. Seventy-three patients had a histologically verified CD; 37 of them had been treated by ileocolic resection. The remaining 31 patients examined after clinical and laboratory examinations revealed a high degree of suspicion of CD. C-reactive protein was elevated relative to reference values (normal $<0.5$ mg/dL) in 17 patients after ileocolonic resection (46%), in 25 Crohn’s patients without resection (69%), and in 16 patients with a high degree of suspicion of CD (52%).

Complete endoscopic evaluation of the colon with intubation of the terminal ileum and histologic examination through the ileocecal valve or an ileocolonic anastomosis was achieved in 96 patients (92.5%). Reasons for incomplete ileocolonoscopy were disease severity ($n = 1$), stenosis ($n = 4$), or technical impossibility ($n = 3$). Tolerance of MR examination was in general very good. The average duration of the entire MR examination within the MR imaging unit was approximately 36 minutes. Sufficient ileum distension was achieved in all patients and provided good diagnostic quality for assessment.

According to the endoscopic examination, stenosis (Fig. 1) was present in 26 patients (25%) and could be ruled out in 78 patients (75%). Total agreement between MR and ileocolonoscopy could be reached in 74 patients (71%). Eight times MR overestimated the degree of stenosis when compared with endoscopy, whereas in 22 patients MR underestimated pathology (Table 1). The test by Bowker revealed a significant difference between the 2 modalities ($P = 0.0061$). The most important differences between MRT and endoscopic scoring were found in the group of 37 patients after ileocolic resection (Table 2).

Finally, a subgroup histology was used as the gold standard for distribution and severity of inflammation ($N = 82$). Histology indicated absence of inflammation in 50 patients (48%). MR and endoscopic findings were concordant in 38 patients (76%) and 37 patients (74%), respectively. Both imaging modalities detected slight inflammation in 10 patients (20%). Endoscopy assumed severe signs of inflammation in 4 patients (8%). Overall, there were 38 true-negative, 27 true-positive, 3 false-positive, and 14 false-negative results by MRT (sensitivity, 65.9%; specificity, 76%). Corresponding results by ileocolonoscopy were 37 true negative, 29 true positive, 4 false positive, and 12 false negative (sensitivity, 70.7%; specificity, 74%).

Additional findings were obtained in 25 patients by MRT. Nineteen patients showed pathologically enlarged lymph nodes (>15 mm) in the area of the inflamed bowel segment, 3 patients presented with inflamed bowel segments above the terminal ileum (2 times severe inflammation with stenosis), 1 patient had a fistula, and in 2 patients intra-abdominal fluid collections could be verified.

<table>
<thead>
<tr>
<th>TABLE 1. Assessment of Stenosis ($N = 104$)</th>
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<td>MRT</td>
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Scoring according to simple endoscopic score for Crohn’s disease: 1 indicates no stenosis; 2, low grade stenosis; 3, medium grade stenosis; 4, high-grade stenosis.

MRT indicates magnetic resonance tomography.
TABLE 2. Assessment of Stenosis in Patients After Ileocolic Resection (N = 37)

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<th>Ileocolonoscopy</th>
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Scoring according to simple endoscopic score for Crohn’s disease: 1 indicates no stenosis; 2, low grade stenosis; 3, medium grade stenosis; 4, high-grade stenosis. MRT indicates magnetic resonance tomography.

DISCUSSION

Several diagnostic techniques in the past few decades, particularly in the field of imaging technology, have improved the diagnosis of CD, allowing us to evaluate its extent and diagnose its complications earlier.

MR enterography is a relatively new imaging technique that combines improved spatial and temporal resolution with large amounts of ingested neutral contrast material. Advantages of MR enterography for the evaluation of CD include its noninvasive nature, lack of ionizing radiation, and multiplanar projections. The multiplanar projections improve anatomic presentation of the bowel and can help clarify the presence of extramural complications.

Recently, ultra-high-field strength body 3.0-T MR systems have been installed worldwide and are being increasingly applied in clinical practice. The development of dedicated receive coils and increased gradient performance have improved substantially over the last few years, allowing almost all standard MR examinations to be performed on a 3.0-T MR system. The use of a 3.0-T unit has certain advantages over the use of the standard 1.5-T system, including an expected 2-fold increase in signal-to-noise ratio, which contributes to higher spatial resolution or, alternatively, to increased temporal resolution with use of parallel acquisition techniques. Specifically, parallel acquisition imaging allows a reduction in the number of phase-encoding steps, which result in a decrease in imaging time and an increase in temporal resolution. The improved spatial resolution at high magnetic field strengths is a function of increased signal-to-noise ratio, which allows smaller pixels and thinner sections for a given field of view. Although the benefits of 3.0-T MR imaging for brain and musculoskeletal examinations are well recognized, the benefits for abdominal MR imaging have thus far not been well established. As a matter of fact, several issues must be considered when applying 3.0-T MR in the abdomen, including the alteration of the radiofrequency field and relaxation time, increase in energy deposition and susceptibility effects, and problems associated with motion artifacts.

In numerous studies, the diagnostic efficiency of the 1.5-T magnetic resonance tomography (MRT) was correlated with different investigation methods (endoscopy, sonography, computer tomography, and double balloon enteroscopy).

In a comparison between capsule endoscopy and MRT, it became clear that significantly more inflammatory lesions in the proximal small intestine and the mid small intestine are discovered through capsule endoscopy. In a pilot study in 2007, Seiderer et al examined to what extent the results of double balloon enteroscopy correspond with the results of MRT in patients with suspected CD. Both investigation methods complement each other well and have the potential to establish themselves as diagnostic standards.

In a study by Florie et al from the year 2005, which focused on the severity of the disease, 1.5-T MRT was compared with ileocolonoscopy on the basis of the Crohn’s disease endoscopic index of severity of 31 patients. The highest agreement was found in the “terminal ileum” segment of the intestinal tract ($r = 0.63; P < 0.001$).

This study evaluates 3.0 high-field MR technology in the terminal ileum in a large sample.

Already in 2006, Gemert-Horsthuis van et al examined the activity of CD in a group of 20 patients with the 3.0-T MRT. The disease activity was classified using the Crohn’s disease endoscopic index of severity and compared with the ileocolonoscopy results. In 10 of 13 cases, the tomographic evaluation corresponded to that of the ileocolonoscopy. It was therefore confirmed that it is possible to use abdominal 3.0-T MRT for diagnosing CD.

To increase osmolarity, we used the 2.5% mannitol solution recommended by Schunk et al. As intravenous contrast agent before the T2-weighted test series, we chose the paramagnetic agent Omniscan, which has excellent contrast and pharmacodynamic properties. Several studies have confirmed this.

Approximately 20 seconds passed between the intravenous application of the contrast agent by means of a high-pressure syringe and the start of the measurement. The preparatory examinations showed that at that time a maximum amount of Omniscan had reached the gastrointestinal tract, providing optimal conditions for evaluation. With the exception of an occasional sensation of heat, patients did not experience problems due to the application of the contrast agent. This is consistent with the results of a study by Runge et al in which the behavior of MR

FIGURE 2. Normal study showing a thick slab T2-weighted fat-suppressed coronal image.
contrast agents was examined. According to this, the currently approved MR contrast agents are generally very safe and have few side effects. The Omniscan we used causes fewer anaphylactic reactions than the other available contrast agents and leads to less tissue damage when injected paravasally.

The selection of sequences was developed by the manufacturer after extensive preparatory work and measurements on healthy subjects and recommended to us. We used the standardized order.

This special examination protocol, including careful preparation of patients, created the prerequisites for evaluating changes in the intestinal wall. Motion artifacts due to respiration and peristalsis have to be eliminated and uniform distension of the small intestine and large intestine has to be achieved. The reduction of motion artifacts is achieved by using fast sequences, which enable data acquisition while the patient is not breathing, and through hypotension of the intestine induced by means of Buscopan. T₁-weighted gradient echo sequences and T₂-weighted TSE sequences were used. Shoenut et al²² have been able to achieve results equivalent to those of endoscopy by employing a 2-dimensional FLASH sequence without intestinal contrast.

The single-shot TSE sequences in T₂ weighting used in our procedures (Fig. 2) were originally employed in MR cholangiography and MR urography. The advantage of these sequences is that because single sections can be imaged in 1 second, motion artifacts are reduced to a minimum. Lee et al²³ were therefore able to successfully use these sequences in small intestine diagnostics.

In a study from the year 2006, Maccioni et al²⁴ examined and compared T₁-weighted, gadolinium supported MR sequences and came to the conclusion that both sequences correctly recognize mural and transmural inflammations of the intestinal wall and that in combination they are very useful for diagnosing CD.

The comparison of the stenosis parameter between ileocolonoscopy and MR therapy shows significant differences (P = 0.0061).

This result is caused by the method and can further be explained by the differentiation into individual patient groups. Group I (patients with suspected CD) showed good agreement between MRT and ileocolonoscopy. “No stenosis” was diagnosed by both procedures in 90.6% (n = 29/32). This suggests a high specificity of the MRT for patients with suspected CD (for the stenosis parameter) and falls in line with a study by Ajaj et al²⁵ from the year 2005, which emphasized the high specificity of MRT in the intestinal area. Furthermore, in this patient group, both methods completely correspond in the diagnosis of nonpassable stenosis. In patient group I, minor deviations of only 1 grade for the stenosis parameter were found in only 2 patients. The large differences between the 2 examination methods for the stenosis parameter can therefore not be attributed to the examination results of group I. Considerable deviations in the findings for the stenosis parameter are primarily found in patient group III (patients after ileocolic resection). Due to their disease patterns, this was the patient group in which the highest overall number of stenoses was diagnosed. In this patient group, ileocolonoscopy showed a tendentially higher sensitivity. In 35.1% of patients, the stenosis could not be passed with an endoscope and was therefore classified as “severe.” In comparison, only 5.4% of the patients were diagnosed with severe stenosis on the basis of the MRT examination. One reason for this is the usually severely scarred and stenosed colon of the patients after surgical resection. Procedurally, it can be difficult for the endoscopist to make a precise statement regarding the type of stenosis. A similar problem, which is mainly attributable to methodology, can be found in studies on capsule endoscopy, which is useful in diagnosing patients with suspected CD but should not be used in patients with known or suspected stenoses.²⁶,²⁷

In order to keep this procedural error to a minimum and to not further influence the test results, those results which could not be assessed were not evaluated for subsequent parameters. In case of a nonpassable stenosis, ileocolonoscopy, for example, cannot provide further information regarding the degree of inflammation and possible fistulas. As a matter of fact, it has to be noted that this clear methodological advantage of the MRT examination was of great use in at least 20 patients (19.23%, N = 20/104). For these patients, statements regarding the location of stenosis, the degree of inflammation in the terminal ileum, and possible existing fistulas were possible solely on the basis of the MRT results.

For the “length of stenosis,” no significant differences were found between the ileocolonoscopy examination and the MRT (P = 0.1736). The MRT can therefore be considered a means equivalent to ileocolonoscopy with regard to the evaluation of stenosis length. The correct assessment of stenosis length is of great importance, particularly with a view to possible surgical therapy options. Stricturoplasty is the method of choice in the case of multiple, serial stenoses of the small intestine, the resection of which would result in a loss of relatively large parts of the colon, whereas laparoscope-assisted ileocolic resection is the method of choice for stenoses with a large longitudinal diameter.

This study confirms the high value of the hydro-MRT in diagnosing ileitis terminales. Both methods are in good agreement (P = 0.1102), emphasizing also the role of contrast agent accumulation in the inflamed intestinal wall as a parameter for evaluating inflammatory activity. The theoretical advantage of a macroscopic assessment of the mucous membrane in the context of the ileocolonoscopy did not result in a diagnostic advantage in this study. This is in agreement with various studies in recent years, which showed a correlation between contrast agent accumulation in the intestinal wall and the degree of inflammation.²⁹,³⁰

Although the diagnosis of fistulas is traditionally a domain of MRT, with a test result which lies even above the defined significance level (P = 0.0833), this study shows that ileocolonoscopy is also accurate in diagnosing fistulas.

The highest number of matches (100%) was found in patient group I (patients with suspected CD). As expected, however, MRT was clearly superior to ileocolonoscopy in patient group III, in which diagnosis of a fistula by means of the endoscopic examination was not possible in 13.5% (n = 5/37) of the patients.

The results of this study regarding the application of ultra–high-field MRT in diagnosing CD in the area of the terminal ileum are promising. The MRT—also in the ultra–high-field area—shows good agreement with the ileocolonoscopy, especially in patients with suspected CD. In addition, it constitutes a useful supplement to an endo-
scopic examination. This could especially be of benefit to patients who have undergone ileocolic resection, whose neoterminal ileum cannot be viewed with an endoscope due to cicatrical stenosis.

The lacking of possibility to take a biopsy is a clear disadvantage of MRT diagnostics; nevertheless, one finds a high congruence in the assessment of inflammation in comparison with histology. Nevertheless, MR enterography sometimes reveals incidental findings independent of the endoscopic and histologic results.11

CONCLUSIONS

Body MR imaging at 3.0 T is still in its infancy and will improve substantially over the next several years. In spite of several limitations based on the laws of physics, most patients can undergo an abdominal MRI study at 3.0 T with a reasonable outcome in terms of image quality. As a matter of fact, MR enterography with a 3.0-T scanner is a powerful tool in the evaluation of ileal diseases. The capacity to help accurately determine the severity and extent of CD has made MR enterography the first-line modality at our institution in patients with suspected IBD.

REFERENCES