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Alimentary Tract

Structural bowel damage in quiescent Crohn's disease☆

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ABSTRACT

Background: Crohn's disease is associated with accumulation of progressive structural bowel damage (SBD) leading to the development of stenotic and penetrating complications. The data pertaining to the course of progression of SBD is scarce. The Lemann index (LI) is a novel tool for evaluation of SBD that incorporates pan-enteric clinical, endoscopic and imaging data.
Aims: To evaluate the progression of SBD in quiescent CD patients.
Methods: Patients with known quiescent small bowel Crohn's disease (CD) for at least 3 months (CDAI < 220) were prospectively recruited and underwent repeated magnetic resonance enterographies (MRE) and video capsule endoscopies (VCE). Patients were assessed for SBD on initial and follow-up evaluation using relevant clinicopathological data, MRE and VCE results. Significant structural bowel damage (SBD) was identified as LI > 4.8, and progression of SBD as LI > 0.3.
Results: Sixty one patients were enrolled in the study. Significant SBD was detected 13 (21.4%) on enrollment. Duration of disease ($p = 0.036$) and history of CD-related surgery ($p = 0.0001$) were associated with significant BD. Forty one patients underwent a follow-up MRE (14.8 ± 2.5 months apart). LI was similar at baseline and follow-up. There was a negligible change in LI between the evaluations.
Conclusions: In patients with quiescent Crohn's disease, structural bowel damage was stable over a median of 14 months follow-up.

1. Introduction

Crohn's disease (CD) is characterized by a chronic progressive course that is frequently associated with accumulation of structural bowel damage potentially leading to a development of structuring or penetrating complications. Up to 60% of CD patients will eventually develop complications necessitating surgical intervention [1]. However, it is clear that need for surgery is merely the "top of the iceberg" as far as bowel damage in CD is considered, and is preceded by gradual accumulation of more subtle evidence of ongoing destructive process. Until recently, no quantitative tools for assessment of bowel damage in CD were available. The Crohn's Disease Digestive Damage Score (Lemann index (LI)) incorporates surgical, endoscopic and imaging findings from all segments of the digestive tract into one composite score [2,3]. Within the first 10 years of the disease, at least 2/3 of the patients demonstrate significant bowel damage that is manifested by gradual LI elevation [4]. As recently demonstrated, increasing LI is predictive of subsequent major abdominal surgery; moreover, anti-tumor necrosis factor α (anti-TNF) agents are able to stabilize [5] or reverse BD in some CD patients [6,7]. It is likely that earlier initiation of effective anti-inflammatory treatment at an early phase of the disease before the development of bowel damage may alter the course of CD and prevent future complications [8–11]. This maybe especially important if we take into account a significant diagnostic delay that is characteristic of CD [10,12].

CD is frequently associated with periods of clinical remission that may occur spontaneously and independently of treatment. However, a vast majority of these patients will display at least some degree of mucosal inflammation even when in clinical remission

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[13], and upon scrupulous evaluation of the small bowel with capsule endoscopy (VCE) or magnetic resonance enterography (MRE) significant changes in both disease location and phenotype in comparison to the original evaluation can be detected in over 50% of quiescent CD patients [14]. There is ample clinical evidence supporting the need to treat CD patients to a target of mucosal healing (MH) and not settle for clinical remission, as MH is associated with both durable clinical remission and lower risk of long-term complications [15]. However, the progression of bowel damage in quiescent CD patients is scarcely documented.

Therefore, the aim of the current study was to evaluate the progression of BD in patients with clinically quiescent Crohn's disease.

2. Methods

2.1. Patient population

This study was a sub study of a prospective observational study aimed at detailed evaluation of CD patients with quiescent disease in order to identify clinical, biochemical and endoscopic predictors of pending clinical relapse [13]. The study population included adult (>18 years) CD patients with known SB disease in remission or mild disease symptoms, as determined by a Crohn's disease activity index (CDAI) of <220. All patients were in corticosteroid-free remission for 3–24 months and were treated with a stable medication dose.

The patients were prospectively followed by serial clinical evaluation and biomarker (CRP/fecal calprotectin (FCP) levels) once every 3 months, biannual VCE and annual MRE examinations. Patients were withdrawn from the study if they developed clinical relapse (CDAI > 220) or required a treatment change. All patients signed an informed consent and the study was approved by the institutional ethics review board.

2.2. Study procedures

2.2.1. MRI scans

All MRE examinations were performed using a 1.5T GE Optima MR450w scanner with GEM Suite (GE Healthcare) with oral and intravenous contrast. MR image acquisition was performed using a previously described protocol [16]. SB distention was obtained by using oral contrast: 360 ml of Osmitrol 20% diluted in 1.5 l water. Patients were instructed to drink 4 doses of 465 ml every 15 min an hour before undergoing the MRE examination. During the last 15 min, patients received via infusion 150 ml of saline containing 0.5 mg of glucagon in slow drip. Axial and coronal LAVA sequences were acquired before and 40 s after intravenous administration of Gadolinium. A board-certified abdominal radiologist with 10 years of experience in reading MRE reviewed all MRE examinations.

2.2.2. Capsule endoscopy studies

A patency capsule (PC) test (Given Imaging, Yokneam, Israel) was performed in all patients with active SB disease detected on MRE. If no active SB disease was detected by MRE, a PC study was not performed. If the PC was not eliminated from the SB within 30 h, the patients were withdrawn from the study. In patients with isolated SB CD (L1 by the Montreal classification), SB-III capsule (Given Imaging, Yokneam, Israel) was used. In patients with SB and colonic CD (L3 disease), a colonic capsule (PillCam colonic capsule 2, Given Imaging, Yokneam, Israel) was administered; in these patients, the SB data was reviewed and scored as described for the SB capsule.

The preparation for VCE included intake of clear fluids only for 24 h prior to the procedure and a 12 h overnight fast. For a colonic capsule study, a split-dose PEG preparation was used. An additional fluid bolus was given after 2 h from ingestion of the capsule in order to facilitate small bowel transit. All images were reviewed using the RAPID 8 software (Given Imaging, Yokneam, Israel). The adaptive frame rate mode was activated to ensure visualization of the entire small bowel. Mucosal inflammation was quantified using the Lewis score (LS) [17]. Mucosal healing was defined as LS < 135, mild to moderate inflammation as LS of 135–790, and moderate to severe inflammation as LS ≥ 790 [17].

2.2.3. Inflammatory biomarkers

Fecal calprotectin levels were measured using the Quantum blue calprotectin kit (BÜHLMANN Laboratories AG, Basel, Switzerland). The reported value range is 30–300 μg/g. Levels >100 μg/g were considered positive. CRP levels were considered elevated if >5 mg/l.

2.2.4. Calculation of LI

LI was calculated as previously described [3]. The gastrointestinal tract was divided segments [upper gastrointestinal tract—esophagus, stomach, and duodenum; small bowel—divided into 20 segments of 20 cm; 6 segments for colon and rectum]. Findings at MRE and CE were divided into stricturing and penetrating lesions, scored and adjusted for anatomical coefficients (Supplementary table). Upper GI was scored using capsule endoscopy. For evaluation of the small bowel we incorporated MRE and CE data. Colonic disease was scored using colonic capsule, MRE and the available colonoscopic data. For scoring of resected segments in patients who underwent surgery, original surgical and pathological reports were used in order to calculate the length of resection. Significant BD was defined as LI > 4.8, progression of SBD as ΔLI > 0.3, and regression—as ΔLI < −0.3 [7]. The scores were calculated at both the initial and the follow-up evaluations.

2.3. Statistical analysis

Descriptive statistics were presented as means ± standard deviations (SD) or medians ± interquartile ranges (IQR) for continuous variables and percentages for categorical variables. Categorical variables were analyzed by Chi Square/Fisher's exact test and continuous variables-by Student *t*-test/Mann Whitney test or paired *t*-test as appropriate. A two-tailed p value <0.05 was considered statistically significant. The analysis was performed using IBM SPSS statistic (Version 20.0) (Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

Sixty one patients were enrolled in the study and underwent the initial evaluation; 56/61 (91.8%) were in clinical remission (CDAI < 150) upon enrollment. Twenty five (41%) had normal inflammatory biomarkers; eight (13.3%) had small bowel mucosal healing. Significant mucosal inflammation (LS > 790) was demonstrated in 12/61 (19.6%) patients. Clinical and demographic characteristics of the included patients, as well as treatment at inclusion, are detailed in Table 1.

3.2. SBD assessment upon enrollment

On initial evaluation, the mean LI was 3.7 ± 5.1 (if only patients with available follow-up were included—2.51 ± 3.71). No signs of bowel damage (LI = 0) were detected in 12 (19.6%) of the patients; mild BD (0–4.8) was detected in 36 (59%) of the patients; LI was above 4.8 in 13 (21.4%) of the patients. Duration of disease (8.1 ± 4.8 vs 8.1 ± 4.8 years, p = 0.036) and history of CD-related surgery (69% vs 2.1%, p = 0.0001) were associated with significant SBD. Other clinical characteristics including medical treatment were not associated with SBD (Table 2).

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