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Fecal calprotectin in the prediction of postoperative recurrence of Crohn's disease in children and adolescents☆

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ABSTRACT

Background: Fecal calprotectin (FC) correlates with endoscopic recurrence of Crohn's disease (CD) in adults but has not been studied among children postoperatively. We aimed to analyze whether FC relates with postoperative CD recurrence in children.
Methods: Altogether 51 postoperative endoscopies and FC measurements from 22 patients having undergone surgery for CD at age ≤18 years were included.
Results: Ileocecal resection (n = 15), small bowel resection (n = 6), or left hemicolectomy (n = 1) was performed at median age of 15.1 (interquartile range 14.4–17.6) years. Following surgery, FC decreased significantly (659 vs. 103 μg/g, p = 0.001). During median follow-up of 5.7 (4.2–7.7) years, either endoscopic or histological recurrence occurred in 17 patients (77%). FC >139 μg/g at time of endoscopy or FC increase of 79 μg/g compared to first postoperative value was suggestive of endoscopic recurrence (Rutgeerts score i2-i4), while FC >101 μg/g or increase of 21 μg/g indicated histological recurrence. Best accuracy for prediction of recurrence was obtained by combining FC at endoscopy and the postoperative increase of FC. The corresponding AUROC values were 0.74 (95% 0.58–0.89) for endoscopic recurrence whereas 0.81 (95% CI 0.67–0.95) for histological recurrence.
Conclusion: FC is a useful surrogate marker of postoperative recurrence also in pediatric CD patients.

Crohn's disease (CD) is a chronic relapsing inflammatory disorder of the alimentary tract with a continuously increasing incidence in the pediatric population [1–5]. Compared to adults, childhood-onset CD typically shows a more active disease pattern and greater need for immunosuppressant therapy [4]. Ileum is affected in 70% of children and is prone to stricture and fistula formation, which occur in about 25% of pediatric CD patients [3,4,6]. Resection of the affected bowel segment either because of such complications or for unresponsive luminal disease is performed in 30–50% of pediatric CD patients by young adulthood [4,7] and as many as 70% of operated patients require further surgery during their lifetime [8,9].

Recurrent mucosal inflammation is observed in endoscopy in 70–90% of adult CD patients within a year of surgery although only one third present with symptomatic relapse of the disease [1,8–10]. Histological activity may develop at the site of the anastomosis as soon as after a week of bowel resection [11]. Even though longer postoperative remission periods are reported for children, most studies have monitored clinical recurrence rates instead of endoscopic follow-up [2,12–15]. As clinical symptoms are frequently absent and serum biochemical markers normal until significant inflammatory changes have developed, ileocolonoscopy with histological verification should be considered as the gold standard for assessing disease activity and postoperative recurrence [6,8–10,16].

Calprotectin is a neutrophil-derived protein excreted in stool in abundance in the presence of mucosal inflammation [17–20]. Fecal calprotectin (FC) outperforms serum markers in the detection of bowel wall inflammation and reflects the endoscopic activity of CD reliably in both children and adults [17,18,20–23]. Its concentration has been shown to increase in the presence of histological pouch inflammation following proctocolectomy for ulcerative colitis [24]. In addition, FC levels correlate with endoscopic disease recurrence rates after bowel resection in adult CD patients [8,25], although not all studies have confirmed this association [26,27]. In pediatric Crohn patients, FC has not been evaluated postoperatively and neither has its correlation with histological recurrence been assessed after surgery. We aimed to evaluate

Abbreviations: CD, Crohn's disease; FC, fecal calprotectin; MRE, magnetic resonance enterography; IQR, interquartile range; AUROC, area under receiving operating characteristic; PPV, positive predictive value; NPV, negative predictive value; AZA, azathioprine; TNF, tumor necrosis factor; MTX, methotrexate.

☆ Conflicts of interest: None to declare.

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the postoperative course of FC and its accuracy in the detection of endoscopic and histological recurrence in children and adolescents having undergone bowel resection for CD.

1. Methods

This was a retrospective study including all patients with childhood-onset CD having undergone bowel resection at age ≤18 years as well as postoperative endoscopies and FC measurements in a tertiary care children's hospital during 1994–2015 (n = 22). Patients without follow-up endoscopy and FC data were excluded (n = 7). The diagnosis of CD was based on upper and lower gastrointestinal endoscopies and evaluation of histopathological biopsies in all cases. The medical records including operative, endoscopy, and pathology reports were reviewed. The type of surgery, number of bowel resections, possible postoperative complications as well as medications before and after surgery were recorded.

1.1. Endoscopy data

Altogether 46 ileocolonoscopies, 3 capsule endoscopies, and 2 magnetic resonance enterographies (MRE) (total n = 51) from 22 patients were included. Endoscopies were performed when clinically considered necessary. Endoscopy findings were classified according to Rutgeerts score where remission was defined as i0 (no lesions) or i1 (less than five aphthous lesions) and recurrence as i2 (>5 aphthous lesions or larger lesions confined to anastomosis), i3 (diffuse ileitis), or i4 (diffuse inflammation with large ulcers and/or narrowing) [28,29]. Indications for MRE were follow-up of ileal disease or terminal ileum not reached in ileocolonoscopy. Both examinations showed a clearly strictured bowel segment and were graded as i4.

1.2. Biopsy specimens

Biopsies were taken in ileocolonoscopies from the anastomosis, the ileum, cecum, ascending colon, colon transversum, descending colon, sigmoid colon, and rectum. The specimens were evaluated by pediatric pathologists and the histological findings were graded as quiescent CD (0) if no inflammation or chronic inflammation without active component was present, and active CD (1) if signs of acute inflammation, such as inflammatory infiltration, crypt injury, crypt abscesses, or ulcerations were detected. In total 43 histology reports from 46 ileocolonoscopies were reviewed.

1.3. Fecal calprotectin

FC was measured with quantitative enzyme immunoassay as previously described and expressed as μg/g [30]. Preoperative (n = 17) and postoperative FC measurements (n = 19) were recorded. Follow-up FC samples (n = 51) were included in the study if measured within 6 months of the endoscopy or MRE.

1.4. Statistical analyses

The descriptive results are presented as medians with interquartile ranges (IQR). Spearman rank correlation was used to examine associations between variables. Kruskal–Wallis test and Mann–Whitney U test were used to compare continuous variables, Wilcoxon signed-rank test to compare repeated measurements within groups, and Fisher exact test was applied when comparing frequencies between groups. Receiving operating characteristic (ROC) curves and areas under ROC curves (AUROC) were used to evaluate the ability of FC to detect the presence endoscopic or histological recurrence of CD. The optimal cutoff values were calculated using the maximum sum of specificity and sensitivity. To evaluate the combination of two different parameters for the prediction of CD recurrence, the predicted probabilities from a binary logistic regression model were used to plot the respective ROC curve. The analyses were carried out with SPSS version 22 (SPSS Inc., Chicago, IL) and the level of significance was set at $p < 0.05$.

1.5. Ethics

The study was approved by the ethical committee of Helsinki University Hospital.

2. Results

2.1. Patient characteristics

Altogether 22 eligible patients were identified. Half had extraintestinal manifestations of CD, of which mild arthralgia was the most common. Symptomatic upper gastrointestinal disease was present in one, however, aphthous ulcers were seen in endoscopy in the esophagus of two additional patients. Full medication data were available for 21 patients, of whom 67% (n = 14) had used immunosuppressive medications preoperatively while 33% (n = 7) had not (Table 1).

2.2. Operative details

First bowel resection was performed median 2.2 (1.0–4.2) years after the diagnosis of CD. The strictured or severely affected bowel segment, most commonly the ileocecal area, was removed in laparoscopy (n = 9, 41%) or in open surgery (n = 13, 59%) (Table 2). Urgent or emergency surgery for perforation, bleeding, infection, or occlusion was scheduled in six patients (27%) while others underwent elective operations. Postoperative complications were uncommon (Table 2). Corticosteroids, used prior to surgery in 90% (n = 18), were gradually tapered and discontinued. Postoperative medications were designed individually according to disease behavior and estimated risk of recurrence (Table 2). Postoperative FC, measured median 1.8 (0.75–2.7) months after surgery, was significantly lower when compared to preoperative FC, measured 4.5 (1.5–5.5) months prior surgery (103 vs. 659 μg/g, p = 0.001, Table 2).

2.3. Follow-up endoscopies

Endoscopy or MRE (n = 51) was performed 38 (15–58) months following the latest surgery at the age of 19.2 (17.5–22.9) years. Endoscopic disease recurrence was observed in half of cases while histological recurrence was present in two thirds (Table 3). Patients with endoscopic recurrence were more likely to be on immunosuppressive medication at time of endoscopy compared to those without recurrence (88% vs. 60%, p = 0.025, Table 3). FC at time of endoscopy and the increase of

Table 1
Baseline patient characteristics (total n = 22) and medications used preoperatively.

Sex, n (%)	
Male	7 (32%)
Female	15 (68%)
Median age at diagnosis (years)	13.6 (11.9–14.2)
Extraintestinal manifestations, n (%)	
Arthralgia	9 (41%)
Primary sclerosing cholangitis	2 (9%)
Erythema nodosum	1 (4.5%)
Gallstones	1 (4.5%)
None	12 (55%)
Perianal CD, n (%)	3 (14%)
Medications used preoperatively,[a] n (%)	
AZA	11 (52%)
Anti-TNF-α agents	6 (29%)
MTX	3 (14%)

CD = Crohn's disease, AZA = azathioprine, TNF-α = tumor necrosis factor α, MTX = methotrexate.
[a] Reported for 21 patients.