Pediatric inflammatory bowel disease: Diagnostics, treatment and psychosocial consequences

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CHAPTER 2

The additional value of upper gastrointestinal tract endoscopy in the diagnostic assessment of childhood inflammatory bowel disease

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ABSTRACT

Objectives: For the choice of treatment in children with inflammatory bowel disease (IBD) it is important to make a discrimination between Crohn's disease (CD) and ulcerative colitis (UC). To look for pathognomonic features of CD upper gastrointestinal tract (UGT) endoscopy has become part of routine evaluation of children with suspected IBD. However, pathological changes can also be found in the UGT in patients with UC. The aims of this study were to establish the role of UGT involvement in the diagnostic assessment of suspected IBD in children and to detect histopathological changes in the UGT mucosa which can distinguish CD from non-CD (UC and non-IBD).

Methods: Biopsies (colon, ileum, duodenum, stomach, esophagus) from children suspected for IBD who underwent endoscopy between 2003 and 2008 were reassessed by a blinded, expert pathologist. The histological findings of the UGT were compared with the diagnosis based on ileocolonic biopsies and the final diagnosis.

Results: In 11% of the children with CD the diagnosis was solely based on the finding of granulomatous inflammation in the UGT. Focal cryptitis of the duodenum and focally enhanced gastritis were found significantly more frequent in children with CD compared to children with UC and non–IBD, with a specificity and positive predictive value of 99% and 93% and 87.1% and 78.6%, respectively.

Conclusions: Histology on ileocolonic biopsies alone is insufficient for a correct diagnosis of CD or UC in children. UGT endoscopy should therefore be performed in the diagnostic assessment of all children suspected for IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) consists of two major clinical entities known as Crohn's disease (CD) and ulcerative colitis (UC). In approximately 5-30% of children differentiation between CD and UC is not possible and a diagnosis of indeterminate colitis (IC) is made (1-5). There is no single diagnostic test, as "gold standard", which can reliably distinguish between CD and UC. A definite diagnosis of the type of IBD is based upon a combination of medical history, endoscopic findings, histological abnormalities and radiologic features. In general we state that the inflammatory process in UC is limited to the large bowel, whereas CD may occur throughout the entire gastrointestinal tract including the upper gastrointestinal tract (UGT). Therefore, endoscopy of the UGT might have an important role in the diagnostic assessment of CD in children. However, several reports have shown that pathological changes might also been found in the UGT in UC (6-12). Microscopic mucosal lesions have been identified in biopsies from the UGT in 64%-90% of CD, as well as in 38%-70% of UC patients (6,7,10,11). Most of these findings were non-specific and not helpful in discriminating CD from UC. Even focally enhanced gastritis, as an isolated finding, which is often reported to be suggestive of CD, is neither sensitive nor specific for CD (13). Today, there is still no uniformity on the diagnostic criteria of IBD of the upper tract (14). Only the detection of epitheloid granulomas appears to be the histological hallmark of gastric CD. Therefore the question rises if endoscopy of the UGT is still justified in the diagnostic assessment of childhood IBD, taking into account the higher risk of complications and increased costs (15).

The aims of this study were 1) to establish the fraction of pediatric CD patients whose diagnosis relies on the detection of granulomatous inflammation in UGT and 2) to detect histopathological changes in the UGT mucosa, besides granulomas, which can distinguish CD from non-CD (UC and non-IBD).

MATERIALS AND METHODS

All children suspected for IBD visiting our department of pediatric gastroenterology between January 2003 and December 2008 were included in this study. Presenting symptoms were extracted retrospectively from the medical charts. Due to our standard procedure, all patients underwent both UGT endoscopy and ileo-colonoscopy. Before performing endoscopy a bacterial gastro-intestinal infection was ruled out with a culture of the feces.

All patients had at least one biopsy specimen taken from each part of the colon (cecum, ascending colon, transverse colon, descending colon and rectum), terminal ileum, duodenum, stomach (antrum and corpus) and esophagus. Biopsies were taken from macroscopically normal mucosa and from inflamed areas. The tissue was formalin fixed,

paraffin embedded and routinely processed and stained with hematoxylin and eosin. Each biopsy specimen was cut in two or more levels to increase the chance to detect histopathological changes. Helicobacter pylori (H. Pylori) was detected by both histology and culture from antral biopsies. In this study biopsies from all sites were reassessed by an expert pathologist, who was blinded to the clinical condition and other test results. First, a diagnosis based on ileocolonic biopsies was recorded. Thereafter, a new diagnosis was recorded based on the histological diagnosis of the lower gastrointestinal tract and the presence or absence of granulomatous inflammation in UGT. After all, the final diagnosis was made based on the reference standard procedure, which consisted of endoscopic findings and histopathological interpretation (as described above), imaging studies and on clinical follow-up data and/or repeat endoscopy (table 1) (7,16). Imaging studies, small bowel follow through or contrast enhanced MRI, were performed in all patients without a definite diagnosis based on endoscopic findings and histopathological interpretation of UGT and ileocolonic biopsies. Clinical follow-up data were extracted retrospectively from the medical charts.

Table 1. Diagnostic criteria

Crohn's disease	**Ulcerative colitis**
Non-caseating epitheloid and giant cell granulomas in any part of the gastrointestinal tract Colitis: focal inflammation, submucosal/ transmural inflammation, lymphocyte aggregates (without germinal centers), mucous retention in the presence of more than minimal acute inflammation Ileal involvement not consistent with backwash ileitis Fistulae and/or perianal abscesses Structuring small bowel disease on barium follow-through or MRI-enterography	Absence of features suggestive of CD Colitis: diffuse and mucosal inflammation, crypt distorsion, diffuse globet cell depletion (mucous depletion), increased vascularity
Indeterminate Colitis	**Non-IBD**
Absence of features suggestive of either CD or UC	No histologic features of chronic IBD

All histopathological changes found in the biopsies from the UGT, besides granulomas which were a diagnostic marker, were analysed against the final diagnosis. Focal enhanced gastritis was defined as presence of at least one foveolum/gland surrounded and infiltrated by inflammatory cells. Focal inflammation of the stomach was defined as chronic and/or acute inflammatory infiltrate occurring only in a portion of a biopsy and/or in one biopsy but not in another taken from the same area, without infiltration of foveolae or glands. Focal duodenal cryptitis was defined as chronic and/or acute inflammatory infiltrate with at least one crypt surrounded and infiltrated by inflammatory cells.

Statistical Analysis

Statistical analysis was performed using SPSS (version 18). Because of the relative small sample sizes within groups we used Fisher exact t-tests when comparing categorical variables between groups and non-parametric tests (Kruskal-Wallis) when comparing continuous variables, such as age and duration of disease. The criterion for statistical significance was defined as a P-value of <0.05.

RESULTS

Patient characteristics

A total of 172 children suspected of IBD were enrolled (males: 54%, mean age: 12.3 yr, age range: 1.6-18.1 yr). Based on all available data the final diagnosis was CD in 70 patients, UC in 33 patients, IC in 1 patient and non-IBD in 68 patients. The results of the histological reassessment of ileocolonic biopsies alone, the diagnosis based on all biopsies and the final diagnosis are shown in table 2. Due to the small number of only 1 patient with IC, this patient was not included in the statistical analyses, but also didn't show histological abnormalities in the UGT. No differences were found between the 3 main groups with regard to age at endoscopy and gender. Both duration of symptoms before presentation and follow-up period were significant different between groups (respectively $p=0.03$ and $p<0.0001$). These data and the presenting symptoms are shown in table 3.

Diagnostic yield of UGT endoscopy

Non-caseating epithelioid granulomas in the UGT were present in 21 (30%) children with CD. Granulomas were found in the esophagus in 3 patients, in the stomach in 19 children (antral 10 patients, corpus 5 patients, both in 4 patients) and in the duodenum in 2 children. In all 3 patients with granulomas in the esophagus, granulomas were also found in the colon and the stomach. Non-organised aggregates of histiocytes and Langerhans giant cells in the UGT were seen in 10 (14%) children with CD.

Table 2. Diagnosis based on ileocolonic biopsies, diagnosis based on ileocolonic and UGT biopsies and final diagnosis

	Histology		
Diagnosis	**Ileum/Colon**	**Ileum/Colon + UGT**	**Final diagnosis**
Crohn's disease	**53**	**61**	**70**
	2	**2**	
Ulcerative colitis	**35**	**33**	**33**
	4	**7**	
Indeterminate Colitis	**14**	**10**	**1**
	2	**2**	
Non-IBD	**70**	**68**	**68**

Data are numbers, UGT= upper gastrointestinal tract.

Table 3. Characteristics of the patients

	Final diagnosis		
	CD N=70	UC N=33	Non-IBD N=68
Gender			
Female	26 (37)	17 (52)	36 (53)
Male	44 (63)	16 (48)	32 (47)
Age at diagnosis (years), median (Q1,Q3)	13.1 (10.8-15.4)	13.8 (11-15.6)	12.4 (9.3-15.1)
Duration of symptoms (months), median (Q1,Q3)	4 (2-12)*	3 (2-6)*	6 (3-12)*
Presenting symptoms			
Abdominal pain, no. (%)	60 (86)	30 (91)	54 (79)
Diarrhea, no. (%)	53 (76)*	28 (85)*	23 (34)*
Hematochezia, no. (%)	42 (60)*	30 (91)*	20 (29)*
Weightloss, no. (%)	39 (56)	13 (39)	28 (41)
Growth failure, no. (%)	17 (24)*	2 (6)*	2 (3)*
Nausea, no. (%)	21 (30)*	3 (9)*	11 (16)*
Anorexia, no. (%)	28 (40)	6 (18)	20 (29)
Perianal abscess/fistula, no. (%)	8 (11)	7 (10)	0 (0)
Follow-up period (months), median (Q1,Q3)	57 (37.8-71)*	38 (24.5-52.5)*	8.5 (2.3-40)*

Q1,Q3= first and third quartile, *significant difference between groups, P<0.05.

In 8 children (11%) the diagnosis based on histopathological assessment of the ileocolonic biopsies alone (2 UC, 4 IC and 2 non-IBD) was changed to CD after assessing the biopsies from the UGT (table 2). In these children a granulomatous inflammation was found in UGT: consisting of granulomas (n=5) and non-organised aggregates of histiocytes and Langerhans giant cells (n=3), while the biopsies from the lower gastro-intestinal tract showed no specific features of CD. These 8 children would have been diagnosed wrong if endoscopy of the UGT had not been performed and the diagnosis was based on biopsies from the lower gastro-intestinal tract alone. In eleven patients the diagnosis after histological reassessment of biopsies from the upper and lower gastro-intestinal tract differed from the final diagnosis (table 2 and table 4).

Table 4. Radiology and follow-up data of IBD patients with a different final diagnosis in comparison with the histopathological interpretation

Patient (sex, age)	Histo Dx	Final Dx	Remarks on work-up, radiology and follow-up
M, 14.3 yr	UC	CD	Colonoscopy: ileum not reached, MRI enteroclysis: terminal ileitis
F, 6.9 yr	UC	CD	Follow-up: perianal abscess
F, 15.5 yr	IC	CD	Repeat colonoscopy: focal inflammation, rectal sparing
M, 18.0 yr	IC	CD	Histologic assessment after colectomy: focal inflammation, distal no inflammation
F, 15.5 yr	IC	UC	MRI enteroclysis: normal, follow up 3 yr: good respons to mesalazine enemas
F, 17.8 yr	IC	UC	Follow-up 5 yr: 2 repeat colonoscopies: pancolitis, terminal ileum three times normal
M, 15.3 yr	IC	CD	Follow-up: fistula and stricture of terminal ileum
M, 12.3 yr	IC	CD	Follow-up 2.5 yr: remission induction with nutritional therapy since then no medication
M, 15.8 yr	IC	CD	Colonoscopy: pancolitis, ileum mild ileitis, backwash? MRI enteroclysis: extensive ileitis
F, 12.6 yr	IC	CD	Colonoscopy: normal ileum, MRI enteroclysis: terminal ileitis, repeat colonoscopy: granulomatous inflammation
F, 13.8 yr	IC	CD	Colonoscopy: ileum not reached, CT-scan: ileitis, follow-up: peri-anal fistula

Histo Dx= histopathological diagnosis after reassessment of biopsies from ileum, colon and UGT, Final Dx= diagnosis based on endoscopic findings, histopathologic interpretation, imaging studies and on clinical follow-up data and/or repeat endoscopy, M= male, F= female.

Seven patients were diagnosed with IC after histological reassessment of all biopsies, but turned out to have CD as final diagnosis, and two patients diagnosed with UC after histological reassessment of all biopsies turned out to have CD. Two patients diagnosed with IC after histological reassessment of biopsies turned out to have UC as final diagnosis.

Histopathological findings in the UGT (table 5)

Esophageal findings

The presence of esophageal inflammation was significant higher in CD patients compared to children with UC (p=0.008), but was not significant different compared to children with non IBD (p=0.28). Diffuse inflammation, consistent with gastroesopagheal reflux, was similarly found in all three groups. The presence of focal inflammation was significant higher in CD patients compared to the children with non-IBD (11% versus 0%, p=0.006).

Gastric findings

The presence of microscopic gastric inflammation was significant higher (p<0.0001) in CD patients compared to children with non-IBD, but was not significant different compared to children with UC (p=0.19). Several patients had more than one type of inflammation in their biopsies from the antral and corpus mucosa. Focally enhanced gastritis was significantly more frequent seen in patients with CD (69%) compared to UC patients (24%, p<0001) and patients with non-IBD (7%, p<0.0001). The lesions were located in the antral mucosa in 22, in the corpus mucosa in 12 and in both in 27 patients. Specificity and positive predictive value of focally enhanced gastritis in CD were 87.1% and 78.6%, respectively. The lesions in all three groups consisted of a focal accumulation of chronic inflammatory cells (mononuclear cells; lymphocytes and plasma cells), active inflammatory cells (granulocytes; neutrophils and eosinophils) or both types of inflammatory cells. There was no significant difference in composition of inflammatory infiltrates between the groups. Focal and diffuse inflammation occurred more frequently in CD patients compared to non-IBD patients (respectively p=0.002 and p<0.0001), but was found with equal frequency in UC patients (both not significant). The composition of these inflammatory infiltrates was not significantly different between groups. Reactive antrum gastritis, which may point to a bile-associated chemical gastritis, was frequently seen in children with non-IBD (43%). H. pylori infection was found in the biopsies of 10 patients with no significant difference between the groups (3CD, 3 UC, 4 non-IBD).

Duodenal findings

The presence of duodenal inflammation was significant higher in CD patients compared to children with UC and non-IBD. Focal cryptitis was seen significantly more frequent in CD patients (19%) compared to children with UC and non-IBD (respectively 0% and 1%, p=0.008

and p=0.001). Specificity and positive predictive value of focally "cryptitis" in CD were 99% and 93%, respectively.

Table 5. Histopathological findings (without granulomas)

	Final diagnosis				
	CD N=70	UC N=33	Non-IBD N=68	P-value*	P-value**
Esophageal Findings (total)	**50 (70)**	**14 (42)**	**42 (62)**	0.008	NS
Focal inflammation	8 (11)	1 (3)	0 (0)	NS	0.006
- erosions	3 (4)	0 (0)	0 (0)		
Eosinophilic esophagitis	0 (0)	1 (3)	0 (0)	NS	NS
Diffuse inflammation	39 (57)	12 (36)	42 (64)	NS	NS
Gastric Findings (total)	**64 (91)**	**27 (82)**	**41 (60)**	NS	<0.0001
Focally enhanced gastritis	48 (69)	8 (24)	5 (7)	<0.0001	<0.0001
- chronic	12	2	4		
- active	24	1	0		
- chronic-active	12	5	1		
Focal inflammation	16 (23)	6 (18)	3 (4)	NS	0.002
- chronic	7	5	3		
- active	5	0	0		
- chronic-active	4	1	0		
Diffuse inflammation	31 (44)	13 (39)	5 (7)	NS	<0.0001
- chronic	25	10	5		
- active	1	1	0		
- chronic-active	5	2	0		
Reactive (antrum) gastritis	7 (10)	5 (15)	29 (43)	NS	<0.0001
Cryptabscess	5 (7)	0 (0)	0 (0)	NS	0.02
Duodenal Findings (total)	**22 (31)**	**1 (3)**	**3 (4)**	0.001	<0.0001
Focal cryptitis	13 (19)	0 (0)	1 (1)	0.008	0.001
Focal inflammation	5 (7)	0 (0)	1 (1)	NS	NS
Diffuse inflammation	6 (9)	1 (3)	1 (1)	NS	NS
Cryptabscess	2 (3)	0 (0)	0 (0)	NS	NS
Erosions	1 (1)	0 (0)	0 (0)	NS	NS

Data are numbers with percentages in parentheses, * CD patients vs UC patients, ** CD patients vs non-IBD patients, NS= not significant, P<0.05.

DISCUSSION

In our study the diagnosis CD was solely based on granulomatous inflammation of the UGT in 11% of the children. These children would not have been correctly diagnosed without UGT endoscopy. Furthermore, focal cryptitis of the duodenum and focally enhanced gastritis were found significantly more frequent in children with CD compared to children with UC and non-IBD. Of these inflammatory changes focal cryptitis of the duodenum showed a good specificity and positive predictive value of 99% and 93% respectively, whereas the specificity and positive predictive value of focally enhanced gastritis in CD, respectively 87.1% and 78.6%, were less convincing.

The value of UGT endoscopy is still a topic of debate. Performing endoscopy of the UGT increases the procedure's duration, the risk of anesthesia and procedural complications. Moreover, the increased number of biopsies also increases the costs. The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) IBD Working Group has recommended routine UGT endoscopy at initial presentation in every child suspected of IBD (17). In contrast, a report from the working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the Crohn's and Colitis Foundation of America (CCFA) refrained from recommending routine diagnostic use of endoscopy of the UGT in the diagnostic assessment of children with suspected IBD (18). In the published, so far sparse, literature the frequency of pediatric CD patients whose diagnosis relies on detection of granulomas in the UGT ranges between 7% and 20% (7,11,19). Based on the latter data we advise the routine use of endoscopy of the UGT, to start in an early phase the most appropriate treatment.

The number of children with the diagnosis CD based on inflammation isolated to the UGT would increase if besides granulomas, other histological markers for CD could be identified. To date, few studies have evaluated UGT histology in children with suspected IBD at initial diagnostic assessment and compared the histopathological findings in the UGT of CD patients with UC- and non-IBD- patients (6,7,9-11). Approximately two-thirds of all patients with CD and half of those with UC have microscopic mucosal lesions in the UGT (6,10,11). However, it remains controversial whether the frequently found non-specific microscopic UGT lesions are of clinical relevance for the IBD-patient. To our knowledge, this is the first study showing that focal duodenal cryptitis differentiates between CD and UC or non-IBD. In two other pediatric studies cryptitis of the duodenum was reported in respectively 26% (10) and 8% (20) of children with CD but was not seen in UC or non-IBD patients, but due to the small number of patients in both studies the difference between groups did not reach statistical significance.

Furthermore, our study shows that focally enhanced gastritis supports the diagnosis of CD, but does not reliably differentiate between CD and UC or non-IBD. This finding corresponds with the study of Sharif et al (13). Oberhuber et al. found that focally enhanced gastritis was present in 76% of adult patients with CD compared to 0.8% of healthy controls (21).

Our data should be interpreted in the context of the following limitations: First of all, data were collected retrospectively. However, IBD is a disease without well-defined diagnostic criteria and no diagnostic gold standard exists. Due to the retrospective design we were able to integrate clinical, endoscopic, histological and radiologic features and use the final diagnosis as our reference standard. We used stringent criteria to classify our patients and were able to follow all patients for a long period. Furthermore, the non-IBD group is not an average of the general population, therefore the prevalence of inflammation in the UGT may be higher in the non-IBD group compared to the general healthy population. None of these patients developed IBD, or other gastro-intestinal disease, during the follow-up period.

In conclusion, in 11% of the children with CD, the diagnosis was solely based on the finding of granulomatous inflammation in the UGT. These children would have been misdiagnosed if endoscopy of the UGT had not been performed and the diagnosis would have been based on biopsies from the lower gastro-intestinal tract alone. Focal duodenal cryptitis is a significant finding, pointing towards a diagnosis of CD. The presence of focal enhanced gastritis suggests underlying CD, but is not exclusive to this condition. It does not reliably differentiate between CD, UC and non-IBD patients. All other histological findings in the UGT do not differentiate between CD and UC or non-IBD. Therefore, the present study underlines that endoscopy of the UGT is essential in the diagnostic assessment of childhood IBD.

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