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Upper gastrointestinal involvement in paediatric onset Crohn's disease: Prevalence and clinical implications

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Abstract

Background and aims: Our study evaluated the prevalence, the characteristics and implications of the upper gastrointestinal localisation (UGI+) in paediatric Crohn's Disease (CD) patients.
Methods: This prospective study evaluated 45 newly diagnosed CD patients at diagnosis and follow up with respect to CD localisation.
Results: All patients presented CD at the colon and/or ileum. In 24/45 patients (53.3%, 12 F and 12 M) an UGI+ involvement was also found. UGI+ patients had a younger age of onset (10.9 years versus 12.6 years; $P<0.05$). PCDAI at diagnosis was significantly higher in the UGI+ (41 vs. 25 $P<0.01$). UGI+ patients were overall more symptomatic. Pancolitis and extraintestinal manifestations were also more frequent (19/24 (80%) vs. 12/21 (57%) $P<0.01$). Growth was more impaired at diagnosis in UGI+ patients. By the end of the follow-up (mean 3 years, range 2 to 4) no significant difference was found in PCDAI (17 in UGI+ patients vs. 11 in UGI− P = NS), or the number of relapses. Weight and growth catch-up in UGI+ patients were comparable to UGI− ones. However, UGI+ patients required a more aggressive therapeutic approach.
Conclusion: At least half of paediatric onset CD patients have an upper gastrointestinal localisation. UGI+ patients present an earlier onset and a more severe disease. The final outcome does not differ, but UGI+ patients require a more aggressive therapeutic approach.
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1. Introduction

Crohn's Disease (CD) may affect the entire gastrointestinal tract, but upper gastrointestinal endoscopy is currently not included in all diagnostic protocols. It is known that 26–54%[1–5] of the children affected by CD present an upper gastrointestinal involvement when systematically searched for that. However, the exact prevalence and the clinical characteristics and therapeutic implications of an upper gastrointestinal involvement both in adults and paediatrics are unknown and very few prospective studies have investigated this issue.

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In our study we evaluated the prevalence and clinical implications of the upper gastrointestinal localisation in paediatric patients affected by CD.

2. Materials and methods

All the paediatric patients consecutively diagnosed with CD between January 2004 and December 2006, followed by the Paediatric Gastroenterology and Nutrition Department of Paediatric Hospital at the University of Trieste were initially selected and enrolled in the study.

The Study was approved by the Hospital Review Board. Inclusion criteria were diagnosis of Crohn's disease, and having performed both upper and lower endoscopy.

Patients with a history of use of NSAIDs or tetracycline, or affected by GERD, peptic disease, celiac disease, food allergies and fungal infections were excluded from the study.

Subjects enrolled were analysed at the time of diagnosis and during the follow up for sex, age at onset of symptoms, types of symptoms, haemoglobin, serum albumin level, blood inflammatory indexes, severity of the disease, and type and duration of therapy.

CD was diagnosed according to the ESPGHAN criteria.[6] Colonoscopy included intubation of the terminal ileum and multiple biopsies was obtained from all the segments of the lower intestinal tract (ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid and rectum). Upper endoscopy evaluated the oesophagus, stomach and duodenum. Multiple biopsy specimens were collected from all three regions, regardless the endoscopic appearance.

CD involving the upper intestine was defined by the presence of the following lesions: submucosal or transmural involvement (surgical specimen), ulcers, crypt distortion, crypt abscess, granulomas (non-caseating, nonmucin), focal changes (within biopsy), and patchy distribution (biopsies). Isolated gastritis was not considered suggestive of IBD.

The person performing the endoscopy was not the same person that performed the clinical assessment of the patient. All biopsies were evaluated by the same pathologist (VV) that was blinded to the clinical information.

All patients were tested for *Helicobacter pylori*. (CP-Test C.H.R. Heim Arzneimittel GmbH).

The severity of the disease was evaluated through the Paediatric Crohn's Disease Activity Index (PCDAI).[7]

Treatment strategies were recorded. Standard treatment protocols in our centre consider the initial use of enteral nutrition in prepubertal patients with prevalent ileal involvement, associated to steroids in cases with evidence of stenosis. Immunosuppressive agents (AZA, MTX) are used in cases of relapses or steroid dependence at standard dosage. Thalidomide and infliximab are used in patients non responsive to previously mentioned immunosuppressive treatments.

Mean time of the follow up was 3 years (range 2 to 4 years).

Statistical analysis was performed using Open Epi Statistical System.

Results are expressed as median and range. Comparisons between groups were made by χ^2 or Fisher's exact test, as appropriate.

Results were considered significant if P value was <0.05.

3. Results

3.1. Recruitment

All recruited patients were Caucasian Europeans.

Forty-five (88.2%) out of the 51 patients consecutively diagnosed with CD underwent both upper and lower gastrointestinal endoscopy at the time of diagnosis and entered the study (age between 0 and 18 years, 26 males and 19 females). In six patients upper endoscopy was initially not performed because of the patient's refusal or because an upper respiratory problem contraindicated the procedure.

All patients presented macroscopic and microscopic evidences of CD at the colon and/or ileum.

In 24/45 (53.3%) patients an upper gastrointestinal involvement was also identified. Two groups of patients were then identified: 24 patients (12 female and 12 males) with both upper and lower involvement (UGI+) and 21 patients (14 males and 7 females) with positive lower but negative upper gastrointestinal endoscopy (UGI−). Mean Hb value at diagnosis was 10.6 g/dl and 10.9 g/dl respectively in UGI+ and UGI− patients.

Amongst the 24 UGI+ patients none presented exclusive oesophageal involvement. 3 patients had exclusive gastric involvement and 4 exclusive duodenal involvement. 6 patients presented both oesophageal and gastric involvement, 5 both oesophageal and duodenal involvement and the same number presented both gastric and duodenal involvement. One patient presented both oesophageal, gastric and duodenal involvement. Histologic findings of these patients are shown in Table 1.

H. pylori faecal antigen tested positive in 1 case of UGI+ and 1 case of UGI− patients (Table 2).

Table 1 Characteristics of UGI+ and UGI− patients.

	UGI+	UGI−	P
Demographics			
Age at diagnosis(year)	10.9	12.6	**<0.05**
Male/female	12 M/12 F	14 M/7 F	**<0.01**
Signs and symptoms			
Abdominal pain	92%	86%	NS
Vomiting + epigastric pain	54%	29%	**<0.01**
Malaise	33%	9%	**<0.01**
Fever	33%	33%	NS
Diarrohea	92%	71%	**<0.05**
Joint pain	37%	23%	**<0.01**
Perianal disease	25%	9%	**<0.01**
Laboratory findings			
ESR (>50 mm/h)	33%	19%	**<0.01**
CRP (>5 mg/dl)	29%	14%	**<0.01**
Hypo-albuminemia (<2.5 g/dl)	42%	19%	**<0.01**
Severity of disease			
PCDAI at diagnosis	41	25	**<0.01**
PCDAI at the end of follow-up	17	11	NS
Disease localisation			
Ileum	12%	24%	**<0.01**
Colon	8%	19%	**<0.05**
Ileum + colon	80%	57%	**<0.01**

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Table 2 Histologic lesions in relation to localisation of disease as documented by EGDS.

Endoscopic localisation of disease N/24 cases	Number of cases N/24	Ulcers and/or erosions	Oedema and erythema	Granuloma
Oesophageal lesions only	0	0	0	0
Gastric lesions only	3	0	3	2
Duodenal lesions only	4	2	2	2
Lesions at gastric and oesophageal levels	6	4	6	1
Lesions at oesophageal and duodenal levels	5	5	2	1
Lesions at gastric and duodenal level	5	5	5	1
Lesion oesophageal, gastric and duodenal levels	1	1	1	1

3.2. UGI+ versus UGI− at diagnosis

The clinical characteristics of UGI+ and UGI− patients are summarised in Table 1.

UGI+ patients had a younger mean age of onset of CD compared to the UGI− ones (10.9 years versus 12.6 years; $P<0.05$).

PCDAI at diagnosis was significantly higher in the UGI+ group than in the UGI− at onset (41 vs. 25 $P<0.01$).

Vomiting and epigastric pain (13/24 (54%) vs. 6/21(29%) $P<0.01$) and diarrhoea (22/24 (92%) vs. 15/21 (71%) $P<0.05$) were more frequently present at onset in UGI+ patients. There was no difference regarding the frequency of abdominal pain (22/24 (92%) vs. 18/21 (86%) P NS) and fever (8/24 (33%) vs. 7/21 (33%) P NS).

Amongst the extraintestinal symptoms, joint pain (9/24 (37%) vs. 5/21 (23%) $P<0.01$) and perianal disease (6/24 (25%) vs. 2/21 (9%) $P<0.01$) were both more common amongst UGI+ patients.

Pancolitis was also more frequent (19/24 (80%) vs. 12/21 (57%) $P<0.01$) amongst UGI+ patients.

Growth was significantly more impaired at diagnosis in UGI+ patients compared to UGI− patients (Figs. 1–2), both for height ($P<0.05$) and weight ($P<0.05$).

According to the Paris classification for location of IBD[8] all UGI+ patients were L4a classified for upper involvement, whilst low involvement was as follows: 19/24 L3, 3/24 L1, and 2/24 L2.

3.3. UGI+ vs. UGI− at follow up

By the end of the follow-up period no significant difference was found in PCDAI amongst the 2 groups (17 in UGI+ patients vs. 11 in UGI− P = NS), or in the number of relapses (a median of 2 relapses per year in both groups). Weight and growth catch-up in UGI+ patients were comparable to UGI− ones (Figs. 1–2).

However, UGI+ patients required a more aggressive therapeutic approach. The cumulative dose of steroids used in UGI+ patients was significantly higher than in UGI− mean value: 63 mg/kg vs. 45 mg/kg ($P<0.01$).

Immunosuppressive treatments (Azathioprine, Thalidomide, Methotrexate) were more often required to induce and maintain remission, (12/24 (50%) vs. 6/21 (29%) $P<0.01$), and in some cases more than one immunosuppressive drug had to be used (17/24 (70%) vs. 10/21 (48%) $P<0.01$).

UGI+ patients received twice as many Infliximab infusions (mean value: 8 administrations for UGI+ vs. 4 administrations for UGI−).

4. Discussion

A significant number (approximately 50%) of newly diagnosed CD patients in our paediatric series presented with an upper gastrointestinal involvement, which is in accordance with previous reports both in adults and children.[1–5] These patients had a more extensive disease and present a younger age at diagnosis compared to UGI− patients, as already suggested in literature.[7,9–11]

As reported by others, upper CD most commonly involved the stomach, followed by the duodenum and the oesophagus[1] and the most observed mucosal abnormality included oedema, erythema and nodularity of the mucosa followed by ulcers and aphtous.[1,7,12,13] The definition of upper gastrointestinal involvement in Crohn's disease is controversial. Some suggest a more stringed classification in terms of the mucosal alterations compatible with upper CD. On the other hand, according to other recommendations a wider spectrum of microscopic lesions should be considered evidence of upper CD. We have chosen to include several types of mucosal lesions

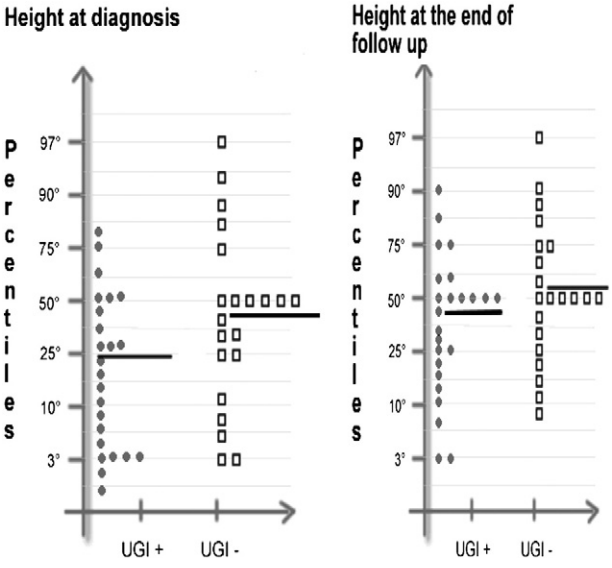

Figure 1 Height percentiles at diagnosis and at the end of follow-up in UGI+ and UGI− patients. The average growth percentile at onset amongst UGI+ was 25°(standard deviation 24°) vs 43° amongst UGI−(standard deviation 30°) with $P<0.05$, whilst at the end of the follow up (average 3 years, range 2–4 years) height amongst UGI+ was 41° (standard deviation 25°), and amongst UGI−52° (standard deviation 27°) with P NS.

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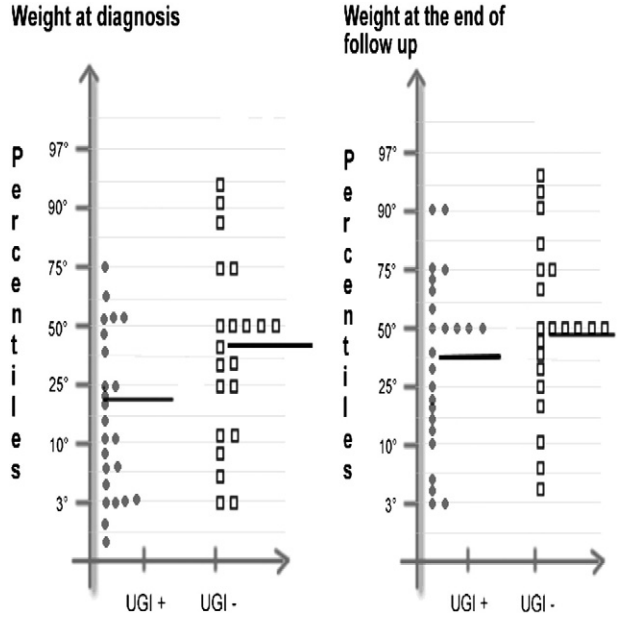

Figure 2 Weight percentiles at diagnosis and at the end of follow-up in UGI+ and UGI− patients. Mean weight percentile at onset was 22° amongst UGI+ (standard deviation 22°) vs. 41° amongst UGI−(standard deviation 29°) with $P<0.05$ whilst weight percentile for the UGI+ was 37° (standard deviation 27°) and 49° amongst the UGI−group (standard deviation 27°) with P NS.

whose presence cannot otherwise be explained amongst paediatric patients.[14–17] Granulomas at the microscopical examinations were found in 9/24 upper gastrointestinal localisations (27%), a rate in the range reported by others.[1,7] In contrast to previous reports, none of the patients described in our series had an exclusively upper gastrointestinal involvement.[1] In other words, upper endoscopy was never decisive in formalising a CD diagnosis.

Whilst UGI+ patients were more symptomatic at onset, the predominant symptoms were nonspecific and not suggestive of a higher gastrointestinal localisation. Therefore, the decision of performing or not an upper gastrointestinal endoscopy should not rely on the clinical picture of the patient, and should be performed in any patient were CD is queried.

Our study is the first one that clearly shows that UGI+ paediatric patients have a greater severity of disease at diagnosis than UGI− patients. UGI+ patients presented with a more severe clinical status and had a significantly higher PCDAI at onset. We cannot exclude that the greater severity of symptoms amongst UGI+ patients could be ascribable to more extensive colonic localisation, rather than an upper GI involvement. Indeed, UGI+ patients had a younger age at onset, which has been shown to be correlated with a more extensive colonic involvement.[18] Overall their growth at diagnosis was more impaired compared to the UGI− group. This might be due to a more extensive lower intestinal disease amongst UGI+ patients, as well as to the fact that the upper intestinal involvement may compromise both the food intake and the intestinal absorption.

UGI+ patients also presented more frequently extraintestinal manifestations of the disease (a fact not reported yet in the literature) as well as perianal involvement, further supporting that the disease was more severe amongst these patients.

Recently, it has been underlined in a cohort of adult Chinese patients that adults with upper gastrointestinal CD have a more aggressive disease characterised by more penetrating and fistulating disease and require more frequent hospitalisations.[19] At our knowledge no follow up study present in literature has evaluated the long term outcome and prognosis of UGI+ vs. UGI− paediatric patients. Our prospective study shows that UGI+ patients not only have a greater severity of disease at onset, but also require a more aggressive therapeutic approach. Indeed, UGI+ patients required more steroids and infliximab infusions compared to UGI− patients. The final prognosis, however doesn't differ between UGI+ and UGI− patients since, even if they required a more aggressive treatment, PCDAI at the end of the follow up was super imposable amongst the two groups. The UGI examination might therefore be useful in planning in advance, and precociously discussing with the family the prospective treatment.

Despite the relatively small sample size of the study, and although our results need to be confirmed in further, more extensive controlled studies, it still represents the first report in literature that suggests that UGI+ children usually have a more severe disease and require a more aggressive therapeutic approach.

In conclusion, in our prospective study more than half of paediatric onset CD patients have an upper gastrointestinal localisation of the disease. UGI+ patients present an earlier onset and a more severe disease activity. Extraintestinal manifestations are more common, as well as a wider colonic extent. The final outcome does not appear different between UGI+ and UGI− but UGI+ patients require a more aggressive therapeutic approach.

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SC carried out the studies and data analyses and drafted the manuscript.

NG carried out the data analyses and drafted the manuscript.

SM participated in the design of the study and coordinated the manuscript drafting.

AV conceived of the study, participated in its design and supervised the manuscript drafting.

All authors have participated to drafting the discussion part of the manuscript and have read and approved the final version of the manuscript.

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