RESEARCH PAPER

Long-term Outcome of Inflammatory Bowel Disease—Unclassified in Children

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Objectives: To document the frequency at diagnosis and evolution over time of inflammatory bowel disease-unclassified in children. **Methods**: Analysis of case records (2004-2011) of patients diagnosed with inflammatory bowel disease-unclassified following upper-gastrointestinal endoscopy, ileocolonoscopy and small bowel imaging. Any subsequent diagnostic reclassification by 2016 was recorded. **Results**: 344 children diagnosed as inflammatory bowel disease: 58% Crohn's disease, 34.5% ulcerative colitis, and 7.5% (*n*=26) inflammatory bowel disease-unclassified. 25/26 inflammatory bowel disease-unclassified patients were followed for 4.5–11.5 years. 17 of these patients needed endoscopic re-evaluation leading to changed diagnosis in ten (Crohn's disease 7, ulcerative colitis 3). **Conclusion**: 7.5% (25/344) of inflammatory bowel disease children had inflammatory bowel disease-unclassified at diagnosis; 10 (40%) evolved into Crohn's disease or ulcerative colitis.

Keywords: *Crohn's Disease, Diagnosis, Ulcerative colitis.*

The revised Porto criteria for diagnosing Pediatric inflammatory bowel disease (PIBD) was published in 2014, and reiterated the need for mandatory upper gastrointestinal endoscopy (UGIE), ileocolonoscopy and small-bowel imaging (preferably magnetic resonance enterography (MRE)) for all suspected cases [1]. The term inflammatory bowel disease unclassified (IBDU) previously termed 'indeterminate colitis', is reserved for cases of colitis where following UGIE and ileocolonoscopy, histological findings are not sufficient to allow a clear differentiation between Crohn's disease (CD) and ulcerative colitis (UC), and small bowel imaging is normal [1,2]. There are no clinical or definitive histological features that are diagnostic of IBDU. However, certain features are more suggestive of IBDU than UC or Crohn's colitis, this is described in the diagnostic features for a child with untreated colitis phenotype in the revised Porto criteria, 2014 [1]. Category 2 features are rare in UC (<5%) and category 3 features are uncommon (<5-10% in UC) while predominance of category 2 features increases the likelihood of CD [1]. Diagnosis of IBDU should ideally be made jointly by Pediatric gastroenterologist and Histopathologist.

The objectives of this study were: (*i*) to document the frequency of IBDU within the total number of children diagnosed with IBD in a regional population; and (*ii*) to document any change to this diagnosis in the long-term.

Methods

Data were collected at endoscopy for all children aged 0-17 years diagnosed as PIBD using the Porto criteria over 7-years (2004-2011). All patients had small bowel imaging (MRE or barium meal follow-through), Ileocolonoscopy and UGIE. Biopsies (2 to 4 per site) were obtained from terminal ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, duodenum, pylorus, stomach and esophagus. Repeat endoscopic assessments were carried out as per clinical indication on patients with persistent symptoms despite treatment.

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All histological specimens were reported by a single specialist pediatric histopathologist both at initial diagnosis and reassessment. Information collected included: age at diagnosis, gender, ethnicity, histological findings, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), inflammatory markers (C-reactive protein, ESR), albumin, liver function tests, full blood count, and urea and electrolytes. Children with a diagnosis of IBDU were managed as per the British Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines [3].

In 2016 (follow-up period of 4.5–11.5 years), clinical notes were examined and data on any change in diagnosis from IBDU to CD or UC, and the histological basis for this change were collected.

RESULTS

A total of 344 new PIBD patients were diagnosed during 2004-2011. ***Fig.* 1** shows the subtypes of PIBD. The mean age at diagnosis was: 11.5 years for CD (*n*=199), 11.6 years for UC (*n*=119) and 10.1 years (*n*=26) for IBDU. The age range of IBDU patients was 1.4 years to 16.1 years; only one child was aged <2 years in whom cow's milk protein allergy had been ruled out.

At diagnosis, blood test results were available for 18 IBDU patients with following mean values: platelet count 460 x 10^9/L (range 142-993), total protein 65 g/L (51-80), albumin 32 g/L (18-43) and hemoglobin 11.3 g/dL (8.8-14.1). One patient had family history of UC. Inflammatory markers (C-reactive protein (CRP) and/or erythrocytic sedimentation rate (ESR) were abnormal in 12/25 (48%) (6 had raised CRP and ESR, 3 had rise in either ESR or CRP). The pANCA results were positive in 11 (44%) patients. It was positive in 4/5 with a revised diagnosis to CD and 2/3 reclassified to UC. The pANCA results were missing for 2 children where diagnosis was revised to CD. There were no significant abnormalities on small bowel imaging at diagnosis in all 25 IBDU cases.

Data were available for 25 out of 26 patients with IBDU; 16 were males (64%) and 9 females (36%). After a minimum 4.5 years and maximum 11.5 years follow-up period, case notes of these patients were examined. Seventeen had been re-evaluated by endoscopic assessment. Eight were in clinical remission, and had not clinically warranted an endoscopic reevaluation. Histological features of the group (Group A) who had revision of diagnosis from IBDU to either CD or UC are highlighted in ***Web Table* I**. Group B consisted of cases without revision of diagnosis. There were no significant differences at initial diagnosis in the histology of the eight children who remained in clinical remission as compared to IBDU patients (*n*=7) who needed re-evaluation but had no change in diagnosis.

***Table* I** lists the initial therapeutic interventions used in 25 IBDU patients. Prednisolone use was similar between the two groups (*P*=0.95). Use of aminosalicylates alone suggestive of milder disease appeared to be higher in Group B but this was not statistically significant (*P*=0.49).

The median follow-up to revision of diagnosis was 51 months (range 34-87 months). At follow-up (by 2016) diagnosis of IBDU had changed in 10/25 (40%) cases; 7 to CD and 3 to UC. Two of these 10 patients required hemicolectomy (1 CD, 1 UC). Preoperative assessment endoscopy was considered inappropriate in these two patients as they were too sick. Detailed histological results were not available for three patients (2 transferred to their local hospital's adult gastroenterology services and 1 migrated to another region).

DISCUSSION

In this study from a single Pediatric gastroenterology center strictly following Porto diagnostic criteria, IBDU comprised only 7.5% (26/344) of total IBD patient at initial diagnosis. Children with IBDU were younger than those with CD or UC and there was male preponderance. After a median follow-up period of 52 months, the diagnosis of IBDU needed revision in 10 (40%) children; 7 to CD and 3 to UC.

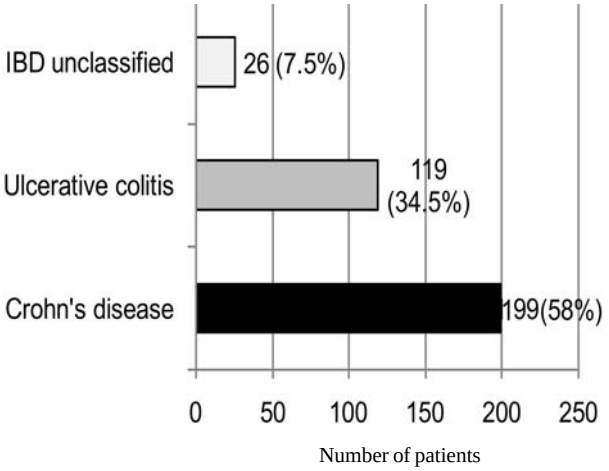

FIG. 1 *Subtypes of pediatric inflammatory bowel disease cases over 7 years (n=344).*

TABLE I THERAPEUTIC INTERVENTIONS USED AT INITIAL DIAGNOSIS

Nature of intervention	*Group A (n=10)*	*Group B (n=15)*
Aminosalicylates alone	2	7
Exclusive enteral feeding alone	0	1
Prednisolone alone	3	3
Prednisolone + Aminosalicylates	3	1
Prednisolone + Azathioprine	2	2
Prednisolone + Exclusive enteral feeding	0	1

Group A: Patients in whom, the diagnosis was revised from Inflammatory bowel disease- unclassified to Crohn's disease or ulcerative colitis; Group B: Patients in whom, the diagnosis of inflammatory bowel disease-unclassified was not revised on follow-up

WHAT THIS STUDY ADDS?

- This study documents a low frequency of IBDU at diagnosis of PIBD
- Around 40% of IBDU cases can evolve into CD or UC over long-term where the diagnosis is made as per Porto criteria and the initial frequency is low.

The study had some limitations. It included review of clinical notes in 2016 (4.5-11.5 years after initial diagnosis of IBDU), and was not a continuous longitudinal study. Some data were missing from the clinical notes, and thus unavailable for final analysis. Some blood results were not available as patients referred from secondary care hospitals had initial investigations done locally. Testing for Anti-Saccharomyces cerevisiae antibodies was not offered by our laboratory. For three patients who had moved to other centers, only summaries of change of diagnosis but not detailed histology following repeat endoscopic assessment were available

Previous studies have recorded much higher proportion (12.7-22%) of IBDU out of total PIBD patients [4,5]. The frequency of IBDU in our series was much lower (7.5%), and is in concordance with only one recent multicenter European study with 3641 children with IBD diagnosed using the Porto criteria (EUROKIDS Registry) where IBDU frequency at initial diagnosis was 7.7% [6]. These low percentages in our study and EUROKIDS study are likely to be a reflection of strict adherence to the Porto criteria for diagnosis of PIBD. In our study, over time, IBDU decreased from 7.5% to 4.3% which is similar to the EUROKIDS study where IBDU decreased to 5.6% during a median follow-up of 5.7 years [6]. A retrospective US study carried out pre-publication of the Porto criteria with 78 IBDU children, documented a lower age at diagnosis [9.2±4 years], and 23% IBDU were reclassified: 8 CD, 5 UC, and 5 non-IBD conditions [7]. A 6-center retrospective study with 210 PIBD patients, IBDU was reclassified in 8/20 (40%) patients, median time to revision was 18.5 months [8]. In our study, use of prednisolone and aminosalicylates at initial diagnosis was similar between those whose diagnosis changed (Group A) and those whose diagnosis remained unchanged (Group B). A retrospective multicenter study which pooled data on roughly equal numbers of patients with CD, UC and IBDU, 260/797 had IBDU [9]. These IBDU patients had milder disease course, with lower medication burden and need for surgery [9].

Our study suggests that it is essential to strictly follow the recommended Porto criteria for optimizing diagnosis of IBD and specially IBDU. Early repeat reassessment with endoscopy and small-bowel imaging in cases with persistent symptoms or where surgery may be a possibility should be considered. As treatment of CD and UC differs considerably, the treatment for changed correct diagnosis is essential.

Contributors: SPP: study design, data collection, analysis, manuscript preparation and revision; BKS: concept, supervision, manuscript editing and revision, and provided expert opinion.

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WEB TABLE I HISTOLOGICAL FEATURES AT DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE- UNCLASSIFIED AND CHANGE OF DIAGNOSIS TO CROHN'S DISEASE OR ULCERATIVE COLITIS

Patient number	*Initial endoscopy and histology*	*Treatment initiated after initial diagnosis*	*Repeat endoscopy and histology*	*Outcome of repeat assessment*	*Time to change of diagnosis*
1	Lower gastrointestinal biopsies including rectal biopsies mild to severe patchy colitis. Esophageal biopsy shows minimal patchy chronic inflammation with no evidence of erosions or ulcers. No granulomas seen. Terminal ileum, gastric and duodenal biopsies normal.	Mesalazine, Prednisolone	Terminal ileum normal. Caecum mild active inflammation. Colon and rectum diffuse colitis with moderate activity. Upper gastrointestinal biopsies normal.	Ulcerative colitis	66 months
2	Mild to moderate active inflammation seen in stomach and colon. No granuloma seen. Gastric specialised and non-specialised mucosa shows patchy chronic inflammation with focal mild activity. Caecal and colonic biopsies show patchy chronic active colitis with mild focal distortion of the surface epithelial architecture. There is focal cryptitis, crypt abscess formation and active inflammation in the surface epithelium and lamina propria.Esophageal and duodenal biopsies normal.	Prednisolone	Distal and terminal ileal biopsy and terminal ileum showed granuloma but no active inflammation. Caecal, colonic and rectal biopsies showed diffuse active colitis and granuloma in ascending colon. Gastric biopsy showed chronic active gastritis with activity.	Crohn's disease[Ileo-colectomy needed 5 years after change of diagnosis]	34 months
3	Rectal biopsy shows diffuse chronic proctitis with moderate activity in form of crypt abscesses. There is goblet-cell depletion. A rare giant cell is noted close to a ruptured crypt. There is no granuloma. Gastric body biopsy shows chronic gastritis with moderate activity. Esophageal, duodenal and sigmoid colon biopsies were normal.	Mesalazine, Prednisolone	Done by adult gastroenterologists in a different hospital	Crohn's disease	52 months
4	Caecal, colonic (ascending, transverse) and rectal biopsies show distortion of surface epithelium and crypt architecture with cryptitis and crypt abscess formation. There are no granulomas. Descending	Mesalazine	All colonic biopsies show similar appearances with active cryptitis. There are no granulomas or giant cells. Rectal biopsy shows mucosal ulceration.	Ulcerative colitis [Sub-total colectomy performed and led to change of diagnosis]	87 months

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Patient number	*Initial endoscopy and histology*	*Treatment initiated after initial diagnosis*	*Repeat endoscopy and histology*	*Outcome of repeat assessment*	*Time to change of diagnosis*
	colon biopsy shows an aphthous ulcer. The gastric biopsy shows mild patchy chronic gastritis.				
5	Colonic biopsies show focal crypt architectural distortion, cryptitis, crypt abscesses and diffuse chronic inflammation. There are no granulomas. Rectal biopsies show focal crypt architectural distortion, cryptitis, crypt abscesses and diffuse chronic inflammation but no convincing granulomas. Esophageal biopsy showed focal chronic inflammation in sub-epithelial. Gastric body mucosa showing patchy chronic inflammation with lymphoid aggregates and giant cells in the lamina propria. There was no significant active inflammation, erosion or granuloma.	Olsalazine	Colonic serial biopsies showed patchy mild active chronic inflammation. Rectal biopsy showed no granulomas but the lamina propria contains two multinucleated giant cells.Gastric body biopsy showed patchy mild chronic inflammation with an isolated multi-nucleated giant cell. Gastric body biopsy showed mild chronic inflammation.	Crohn's disease	79 months
6	Colonic biopsies showed distortion of the crypt architecture and surface epithelium with surface exudate and cryptitis. The lamina propria showed chronic active inflammation, but there are no granulomas. Gastric antrum mucosa shows patchy mild chronic inflammation. No *Helicobacter* or granuloma seen. Duodenal biopsy showed mild oedema and possible villous blunting.	Prednisolone, Azathioprine	Moderate active chronic inflammation involving the ascending and transverse colon. No granulomas or multinucleated giant cells are observed. Descending colon mucosa showed piece of granulation tissue.	Crohn's disease (Sub-total colectomy was performed and led to change of diagnosis)	34 months
7	Ileal biopsy showed active ileitis. Caecal biopsy showed mild inflammation. Ascending colon had active colitis with ulceration. Colonic biopsies showed chronic colitis with mild activity. Rectal biopsy showed mild active proctitis.	Prednisolone	Splenic flexure showed moderate to severe chronic active colitis. Other colonic and rectal biopsy showed moderate chronic colitis with mild activity. Severe esophagitis seen, body of stomach show granulamatous gastritis.	Crohn's disease	50 months
8	Mild active chronic inflammation involving stomach, duodenum, caecum and sigmoid, and moderate active chronic inflammation involving rectum. No granulomas are seen.	Mesalazine, Prednisolone	Terminal ileum normal, caecal biopsies mild focal active inflammation. Rest of colonic biopsies were normal. Rectal biopsies showed moderately active chronic	Ulcerative colitis	58 months

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Patient number	*Initial endoscopy and histology*	*Treatment initiated after initial diagnosis*	*Repeat endoscopy and histology*	*Outcome of repeat assessment*	*Time to change of diagnosis*
	There is evidence of inflammatory colitis, which is classified as indeterminate.		proctitis. Gastric biopsies showed mild focally enhanced chronic inflammation.		
9	Caecal, colonic and rectal biopsies – Patchy colitis with mild activity, no granulomas. Ileum – mild focal activity. Gastric biopsies showed chronic gastritis with focal activity, duodenal biopsies showed mild focal activity. Esophageal biopsies normal.	Prednisolone	Done by paediatric gastroenterologists in a different hospital, histology results could not be obtained	Crohn's disease	39 months
10	All colonic biopsies showed increase in lamina propria cellularity, predominantly by plasma cells and eosinophils. Crypt architectural distortion, with bifurcation of crypts, crypt loss and occasional ruptured crypts were noted. No granulomas seen. Collection of histiocytes in the gastric biopsies.	Prednisolone, Azathioprine	Done by adult gastroenterologists in a different hospital	Crohn's disease	37 months