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Pediatric inflammatory bowel disease: experience in a tertiary pediatric center

Ana Močić Pavić, Iva Hojsak, Zrinjka Mišak, Sanja Kolaček*

The aim of the study was to assess the clinical features and diagnostic work-up in patients newly diagnosed with inflammatory bowel disease in our center. We prospectively collected data on all children (N=158) diagnosed with inflammatory bowel disease at our center from January 2004 to September 2012. During the 8.7-year period, 78 (49.4%) children were diagnosed with Crohn's disease, 73 (46.2%) with ulcerative colitis and 7 (4.4%) with indeterminate colitis. Retrospective analysis yielded the following for Crohn's disease: (a) the PCDAI at diagnosis was 29.4 (range 15-60); (b) the most common presenting symptoms were abdominal pain, diarrhea and weight loss; (c) 28 (35.9%) patients had stunted growth already at presentation; and (d) the predominant location was ileocolonic (n=48; 61.5%), perianal disease was found in 37 (47.4%) and upper gastrointestinal tract was affected in 26 (33.3%) patients; and for ulcerative colitis: (a) a significant rise in the incidence was observed in the last two years; (b) the PUCAI at diagnosis was 26.2 (range 10- >65); (c) the most common presenting symptoms were diarrhea and blood in stool; and (d) most patients had extensive disease with either pancolitis (n=40; 54.7%) or extensive colitis (n=10; 13.4%). The role of small bowel follow through was dubious in our hands as it confirmed endoscopically proven terminal ileum involvement in only 31.3% of Crohn's disease patients. In conclusion, no difference was found in the incidence rate of Crohn's disease and ulcerative colitis; moreover, towards the end of the study, more children were diagnosed with ulcerative colitis. Our patients presented with extensive form of the disease. In diagnostic work-up, magnetic resonance imaging enterography should be done whenever possible.

Keywords: inflammatory bowel diseases

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a group of chronic, relapsing inflammatory disorders of the gastrointestinal (GI) tract. Crohn's *disease* (CD), ulcerative colitis (UC) and indeterminate colitis (IC) are the three types of this disease. The exact etiology and pathogenesis of the disease have not yet been fully elucidated. Current evidence suggests that they result from the interaction of abnormal immune response and environmental factors in genetically predisposed individuals (1-3). The peak incidence of IBD occurs between 15 and 25 years of age and starts during childhood and adolescence in even 25% to 30% of cases (4). The incidence of pediatric IBD varies according to the population studied, but in the developed world, many countries have reported an increased incidence in recent decades (5-12). As for the disease phenotype, pediatric IBD significantly differs from the disease with the onset in adulthood. In children, CD typically presents with an inflammatory type and tends to have a more extensive distribution (13, 14). Similarly, UC in pediatric patients is usually more extensive, with pancolitis being the most frequent form (13, 14). To precisely define the pediatric disease phenotype, the IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has published a diagnostic algorithm for children with suspected IBD (Porto criteria) (15), and also adjusted the Montreal classification for pediatric IBD patients (Paris classification) (34). Moreover, a web-based prospective registry (EUROKIDS Registry) including 44 centers from 18 European countries and Israel

* Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, University of Zagreb Medical School, Zagreb, Croatia

Correspondence to:
Ana Močić Pavić, MD, Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Klaićeva 16,
E-mail: amocicpavic@gmail.com

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(our center included) has been established. Prospective collection of anonymous data on all newly diagnosed pediatric IBD patients enabled an audit of the Porto diagnostic criteria (15), as well as better determination of disease phenotype of both CD (18) and UC (17).

As there are no studies reporting epidemiological and clinical characteristics of pediatric IBD patients in Croatia, we aimed to present diagnostic approach and disease phenotype of our patients.

METHODS

Patients

For the purpose of the EUROKIDS registry, we prospectively collected data on all (N=158) newly diagnosed IBD patients evaluated at our department, which is a Referral Center for Pediatric Gastroenterology and Nutrition in Croatia, from January 2004 to September 2012. The data collected referred to the type of the disease, age, gender, symptoms at presentation, diagnostic evaluation, and disease location. The diagnosis of IBD was based on Porto criteria (15) and disease location was based on Paris classification of IBD (34). Colonoscopy was performed in all patients and terminal ileum intubation was successful in 127 (80%) patients on initial endoscopy and in 150 (95%) children on follow up endoscopy. At the diagnosis, 147 (93%) children underwent upper GI endoscopy. Abdominal ultrasound was performed in all children and small bowel follow through (SBFT) in 100 of 158 (63.3%) patients. Disease activity was assessed by the pediatric CD activity index (PCDAI) and by using the pediatric UC activity index (PUCAI) (19, 20).

Anthropometric measurements were performed by the same personnel on the same weight scale and stadiometer. Subsequently, height for age and weight for height standard deviation scores (SDS) were calculated.

Statistics

Differences between categorical variables were assessed by chi-square test. Differences for non categorical variables were assessed by two-tailed Student's t-test for independent samples. For multiple variable samples, one-way analysis of variance (ANOVA) was used. If the difference between groups was significant, *post hoc* analysis using Tukey HSD for homogeneous distribution and Games-Howell test for non-homogeneous distribution were used. P values < 0.05 were considered significant. Statistical analysis was performed using the SPSS 19.0 (Chicago, IL) statistical software.

RESULTS

Patients

During the study period of 8.7 years, a total of 158 newly diagnosed IBD patients were included in the study: 78 (49.4%) with CD, 73 (46.2%) with UC, and 7 (4.4%) with IC. The epidemiological characteristics, laboratory findings, anthropometric measures and differences between groups are presented in Table 1. Symptoms at the time of diagnosis are shown in Table 2. No significant difference was found in the occurrence of IBD in our center during the study period (Figure 1). Results of laboratory work-up are presented in Table 3.

Crohn's disease

In the CD cohort, the disease most frequently (n=48; 61.5%) involved terminal ileum and colon (L3), followed by termi-

TABLE 1. **Difference between groups according to epidemiology, anthropometrics and laboratory findings; *significant difference Crohn's disease *vs*. indeterminate colitis and ulcerative colitis; **significant difference Crohn's disease *vs*. ulcerative colitis; SDS = standard deviation score; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate**

	Crohn's disease (n=78)	Ulcerative colitis (n=73)	Indeterminate colitis (n=7)	*P*
Age, mean (yrs, range)	13 (1.02-17.9)	12.5 (1.2-17.8)	9.2 (5.5-12)	0.116
Gender (male:female)	42:36	37:36	5:2	0.573
SDS height for age, mean	-0.5	-0.2	1.5	0.018**
SDS weight for height, mean	-0.8	0,5	-0.6	0.019*
CRP	43.6	23.2	6.1	0.019*
ESR	37.4	26.6	26	0.005*
Hemoglobin	114.8	121.4	135.3	0.044
Fibrinogen	7	5.1	5.2	0.033*
Albumin	37	39.1	45.1	0.235
Fecal calprotectin	757	2117	ND	0.115
% of non segmented neutrophils	13.3	14.6	7	0.34

nal ileum (with/without cecum involvement, L1) in 23 (29.5%) and isolated colonic (L2) disease in 7 (9%) patients. Upper endoscopy was abnormal and consistent with CD in

TABLE 2. Symptoms at presentation

	Crohn's disease	Ulcerative colitis
Diarrhea	50 (64.1%)	68 (93.1%)
Blood in stool	23 (31.1%)	68 (93.1%)
Abdominal pain	35 (44.9%)	26 (35.6%)
Weight loss	36 (46.2%)	11 (15.1%)
Stunted growth	28 (35.9%)	2 (2.7%)
Extraintestinal symptoms	6 (7.7%)	4 (5.5%)
Perianal disease	37 (47.4%)	0
Lethargy	7 (9%)	3 (4.1%)
Elevated temperature	17 (21.8%)	4 (5.5%)
Aphthae	4 (5.1%)	0
Acute abdomen	6 (7.7%)	0

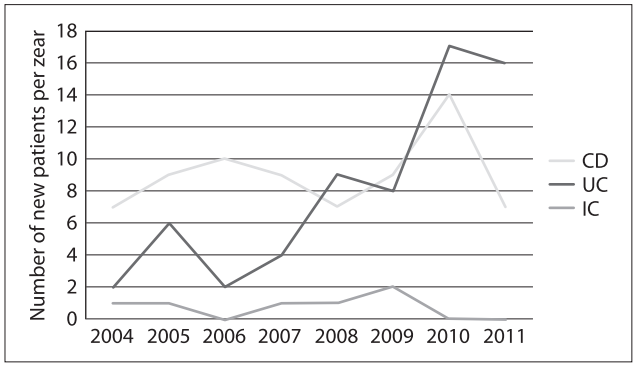

FIGURE 1. Incidence of inflammatory bowel disease (IBD) patients at our center *per* year.

TABLE 3. Incidence of abnormal laboratory results *per* diagnosis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

	Crohn's disease	Ulcerative colitis
Elevated CRP levels	71 (91%)	29 (39.7%)
Elevated ESR	71(91%)	47 (64.4%)
Elevated fibrinogen	46/61 (75.4%)	25/49 (51%)
Elevated fecal calprotectin	30/31 (96.8%)	24/25 (96%)
Low hemoglobin	37/78 (47.4%)	30/73 (41.1%)

26 (33.3%) children, while granulomas were found in only 16 (20.5%) patients. At presentation, the mean PCDAI was 29.4 (median 30, range 10-60); the activity of the disease at presentation is illustrated in Figure 2. SBFT was performed in 70 (89.7%) children; none of the patients with L2 localization had pathologic SBFT, while among those with endoscopically proven terminal ileum involvement only 20/64 (31.3%) had pathologic SBFT. In contrast to these results, magnetic resonance imaging (MRI) enterography, regularly applied since recently (8 patients), was able to confirm all terminal ileum lesions found on endoscopy (7/7). Abdominal ultrasound was performed in all children and found ileal involvement in 61/71(85.9%) children with endoscopically proven terminal ileum involvement.

Ulcerative colitis

Most patients had extensive disease with either pancolitis (E4, n=40; 54.7%) or extensive colitis (E3, n=10; 13.4%), followed by left side colitis (E2, n=14; 19.2%), and proctitis (E1, n=9; 12.3%). At presentation, the mean PUCAI was 26.2 (me-

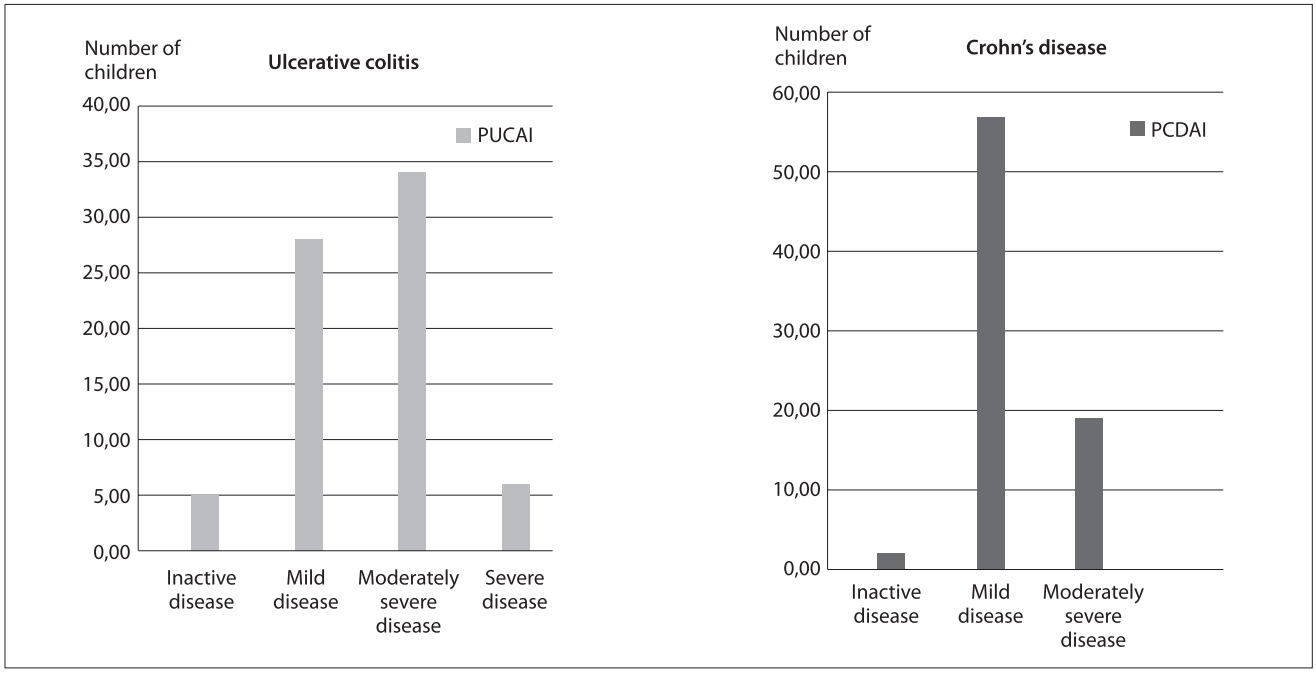

FIGURE 2. Number of patients with disease activity based on Pediatric Ulcerative Colitis Activity Index (PUCAI) and number of patients with disease activity based on Pediatric Crohn's Disease Activity Index (PCDAI).

dian 25, range 10 to >65); the activity of the disease at presentation is shown in Figure 2. SBFT was normal in all children (n=25) who underwent this procedure. Abdominal ultrasound, performed in all children, was abnormal in 18 (24.7%) patients, while in one child terminal ileum was described as thickened, which was not confirmed either by endoscopy or SBFT.

Indeterminate colitis

All children had involvement of the whole colon and in one (14.3%) patient terminal ileum was involved as well. SBFT was performed in 5 children and was normal in all of them, while 2 patients underwent MRI small bowel enterography without pathologic findings. Abdominal ultrasound was performed in all children and was normal.

DISCUSSION

To the best to our knowledge, this is the first report investigating clinical features and diagnostic work-up in newly diagnosed pediatric IBD patients in Croatia. Previously, there were only two Croatian reports, both in adult patients; in the first one from 1991, the incidence rate was 1.5/100 000 inhabitants for UC and 0.7/100 000 for CD, while the second study, which was performed in 2004, found a much higher incidence of 7.0/100 000 for CD and 4.3/100 000 for UC (21, 22). This rising incidence has been reported in many other countries and it is not limited to adult population. In the pediatric age groups, especially in adolescence, the increase in the incidence of IBD and of CD in particular, has been even more pronounced when compared to adult age groups (38). The same results were found in our study, however, while in the first few years, similarly to many other reports (5-12), CD was diagnosed more often, the occurrence of IBD in our center changed in the last two years in favor of UC. Currently, we are not sure if this occurrence will continue, but it has also been described in several other recent reports from Finland, Poland and Italy (37).

Children with IBD may present with a wide range of symptoms in respect to the location, severity and chronicity of inflammation. The most common presenting symptoms in our patients with CD were abdominal pain, diarrhea and weight loss, whilst UC most commonly started with bloody diarrhea. These results are comparable with other European centers (5, 10, 12). Inherent to pediatric IBD patients is growth delay. As a presenting feature, stunted growth was found in one-third of our CD patients, which is in concordance with previous results (23). Growth failure is not only an important sign of active disease but it also presents a significant risk of reduced height in adulthood (39). Therefore, accurate assessment and interpretation of nutritional status, growth, and pubertal status must be part of the treatment strategy for each child with IBD.

In our CD patients, perianal disease was present in almost 50% of cases, which is similar to previous reports on the high incidence, ranging from 25% to 85% (25). As for extraintestinal manifestations, they were found in only 7% of CD and 5.5% of UC cases at the time of diagnosis, which is lower compared to the literature (26) and could be explained with the fact that our data were limited to the first presentation of the disease without the follow-up period.

As for laboratory diagnostic tests, among the several markers of active inflammation measured (erythrocyte sedimentation rate, C-reactive protein, fibrinogen and calprotectin), in our patients, calprotectin was found to be the best indicator. This has also been reported from previous studies, which confirmed calprotectin to be a suitable marker of intestinal inflammation in IBD (36).

However, our results indicate that normal test results are not uncommon and do not exclude the disease, which was also shown by previous studies (27). Therefore, the mainstay of the diagnosis is endoscopy. According to Porto criteria, ileocolonoscopy and upper GI endoscopy are to be performed in all children with suspected IBD. Moreover, in those with CD it is also necessary to establish the extent of the disease. In this study, colonoscopy was performed in all patients and terminal ileum was visualized in 80% of patients on initial and in 95% on follow up endoscopy, while upper GI endoscopy was assessed in 93% of patients. Our results clearly confirmed that in comparison to adults, children have a more extensive disease, involving most of the bowel already at presentation in both CD and UC.

Concerning assessment of the extent of the disease in children with CD, MRI was the only method that could indicate inflammatory changes in the small intestine in all patients. Our study confirmed a very low accuracy of SBFT, which is in concordance with previous reports that found low sensitivity of 59% and specificity of 80% (30-32). Moreover, it has been demonstrated that SBFT is responsible for 16% to 36% of all radiation exposure in children with IBD (16). According to the ESPGHAN and European Crohn's and Colitis Organization (ECCO) guidelines for CD, MRI is recommended as a primary investigation for the visualization of small bowel (33) but the cost and accessibility should be taken into account. Our results strongly support this recommendation to omit the use of SBFT whenever possible.

In conclusion, the diagnosis should be based on good medical history with thorough medical examination including anthropometrics and inspection of perianal region. This should be followed by laboratory tests, although normal results do not exclude the disease. In patients suggestive of

having IBD, diagnostic work-up should include colonoscopy and upper GI endoscopy with biopsies taken from all visualized bowel segments. SBFT should be preferably replaced with MRI enterography or video capsule endoscopy. Early diagnosis leads to timely introduction of medical and nutritional treatment, thereby improving weight gain and linear growth. This diagnostic and lifelong medical care should be led by experienced multidisciplinary team.

Abbreviations:

IBD – inflammatory bowel disease

GI – gastrointestinal tract

CD – Crohn's disease

UC – ulcerative colitis

IC – indeterminate colitis

ESPGHAN – European Society for Pediatric Gastroenterology, Hepatology and Nutrition

SBFT – small bowel follow through

PCDAI – pediatric CD activity index

PUCAI – pediatric UC activity index

SDS – standard deviation scores

MRI – magnetic resonance imaging

ECCO – European Crohn's and Colitis Organization

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Močić Pavić A. – prikupljanje i obrada podataka, pretraživanje literature, pisanje rada/*data collection and analysis, literature search, writing paper*

Hojsak I. – koncept istraživanja, statistička analiza, pretraživanje literature, pisanje rada/*concept of research, statistical analysis, literature search, writing paper*

Mišak Z. – pretraživanje literature, pisanje rada/*literature search, writing paper*

Kolaček S. - koncept istraživanja, tumačenje podataka, pisanje rada/*concept of research, data interpretation, writing paper*

SUKOB INTERESA/*CONFLICT OF INTEREST*

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SAŽETAK

Upalna bolest crijeva kod djece: iskustva tercijarne dječje bolnice

Ana Močić Pavić, Iva Hojsak, Zrinjka Mišak, Sanja Kolaček

Cilj istraživanja je bila procjena kliničke značajke i dijagnostički postupak kod novootkrivenih bolesnika s kroničnom upalnom bolesti crijeva u našem centru. Prospektivno smo prikupili podatke sve djece (n=158) s dijagnozom kronične upalne bolesti crijeva u našem centru od siječnja 2004. do rujna 2012. U razdoblju od 8,7 godina kod 78-ero (49,4%) bolesnika postavljena je dijagnoza Crohnove bolesti, kod 73-je (46,2%) ulceroznog kolitisa i u 7-ero (4,4%) nedeterminiranog kolitisa. O Crohnovoj bolesti: a. PCDAI je iznosio 29,4 (raspon 15-60) u trenutku dijagnoze, b. najčešći simptomi su bili abdominalna bol, proljev i gubitak na tjelesnoj masi, c. 28-ero (35,9%) ih je imalo usporen rast u trenutku dijagnoze, d. najčešća zahvaćenost bolesti je bila ileokolična (48;61,5%), u 37-ero (47,4%) utvrđena je perianalna bolest, dok je kod 26-ero (33,3%) bolesnika bio zahvaćen i gornji dio probavne cijevi. O ulceroznom kolitisu: a. uočen je značajan porast incidencije u posljednje dvije godine, b. PUCAI je iznosio 26,2 (raspon 10->65) u trenutku dijagnoze, c. najčešći simptomi su bili proljev i krv u stolici, d. većina bolesnika je imala pankolitis (n=40, 54,7%) ili ekstenzivni kolitis (n=10, 13,4%). Uloga pasaže tankog crijeva nam je ostala upitna, jer je samo u 31,3% bolesnika s Crohnovom bolesti potvrdila endoskopski utvrđenu zahvaćenost terminalnog ileuma. Nije uočena razlika u pojavnosti između Crohnove bolesti i ulceroznog kolitisa. Štoviše, prema kraju studije više je bilo djece s dijagnosticiranim ulceroznim kolitisom. Naši bolesnici su se prezentirali s ekstenzivnim oblikom bolesti. Preporuka je primjena MR enterografije kad god je to moguće.

Ključne riječi: upalne bolesti crijeva