Inflammatory Bowel Disease Developing in Paediatric and Adult Age

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ABSTRACT

Background and Objective: In recent decades, there has been a significant increase in the incidence of inflammatory bowel disease (IBD). It has yet to be established whether the manifestations of IBD are similar in paediatric and adult ages. The objective of this study was to compare the phenotypic expression of the disease between patients with childhood-onset IBD and adulthood-onset cases, all afferent to the same clinical centre.

Patients and Methods: Descriptive and multivariate analyses were completed on retrospective and prospective data of paediatric-onset and adult-onset consecutive cases who were diagnosed and followed at the same tertiary referral hospital of the University of Padua, Italy, during a period of 14 years (1994–2008). Paediatric-onset patients were further divided into age brackets (0–5, 6–12, and 13–17 year-olds). Analyses were conducted using the SAS package, version 9.1 (SAS Institute Inc, Cary, NC).

Results: Three hundred twelve patients were analysed. At disease onset, the manifestations which were more frequent among the 133 paediatric patients (50.4% with diagnosis of Crohn disease [CD], 43.6% with ulcerative colitis, and 6% with unclassified IBD) with respect to the adult-onset patients were perianal disease (12.8%) ($P < 0.0001$) and extraintestinal manifestations (14.3%) ($P = 0.043$). Among the 179 adult patients (55.3% with diagnosis of ulcerative colitis, 36.3% with CD, and 8.3% with unclassified IBD) instead, severe abdominal pain ($P = 0.008$), diarrhoea ($P = 0.005$), and anorexia ($P < 0.0001$) were more frequently observed. During the follow-up, the presence of extraintestinal manifestations (50.4%) ($P = 0.005$) and perianal disease (44.8% of the patients with childhood-onset CD) ($P = 0.006$) was observed more often in the paediatric-onset group.

Conclusions: In our cases, the phenotypic expression of IBD developing in paediatric age differs from that seen in adults.

Key Words: extraintestinal manifestations, inflammatory bowel disease, paediatric and adult populations, perianal disease

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In the last few decades, there has been a marked increase in the incidence of inflammatory bowel disease (IBD), including Crohn disease (CD), ulcerative colitis (UC), and the unclassified IBD (IBDU), among all age groups in Western populations. This increase appears to have leveled off in adult populations, whereas the figures continue to rise in paediatric populations (1,2). It has yet to be established, however, whether the manifestations of IBD developing in children and adults are similar.

Some evidence on this topic has already been aroused and discussed recently and include the disease extent, which appears to be more extensive among patients with early-onset IBD than among adult-onset cases (3,4); CD behaviour, which evolves more rapidly to stricturing or penetrating disease among the paediatric-onset cases (3,4); the familiarity for IBD, mostly observed among early-onset patients, and its connection with genetics (5); and the different therapeutic management between the 2 age classes (3).

Despite these observations, the common clinical impression of a more severe disease presentation and course among cases of IBD with paediatric onset has not been completely demonstrated. The need of further investigations of this aspect is therefore encouraged.

Recent work by Van Limbergen's group (3) compared children recruited from all the paediatric gastroenterology centres in Scotland with adult patients from 1 gastroenterology department. Our study, instead, is founded on the direct collaboration between the paediatric gastroenterology unit and the adult gastroenterology clinic belonging to the same tertiary referral hospital. The aim of the present study was, therefore, to compare the expression of the disease between patients who developed IBD as children and those whose disease became manifest in adulthood, by analysing data on disease outcome in patients with a long-term follow-up whose IBD first appeared before or after they were 18 years of age.

PATIENTS AND METHODS

The paediatric-onset and adult-onset consecutive cases considered here were diagnosed and followed at the same tertiary referral hospital of the University of Padua, Italy (at the Paediatric Gastroenterology Unit of the Paediatrics Department and at the Department of Surgical and Gastroenterological Sciences, respectively) during a period of 14 years (1994–2008). Each patient has been followed up to the date of the last clinic visit, which occurred before July 2008. The adult patients selected were systematically being cared for at the gastroenterology clinic, that is, at least 1 clinic visit (as outpatient or admission) per year.

All of the patients analysed in the study had a diagnosis of CD, UC, or IBDU, based on clinical, radiological, endoscopic, and histological findings. Information was retrieved from patients' medical records including hospital admissions and outpatient clinic visits. Paediatric-onset patients were further divided into age brackets (0- to 5-, 6- to 12-, and 13- to 17-year-olds) to enable a comparison not only between paediatric- and adult-onset cases but also—and more completely—between different ages of IBD onset in childhood.

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For each patient, the following clinical variables were investigated:

1. Type of onset: "acute" if symptoms of diarrhoea, abdominal pain, and weight loss appeared within less than 1 week; "insidious" when the symptoms appeared during a period of more than 1 week (weeks, months, years)
2. Severity of onset: "mild," "moderate," or "severe" as defined by the activity scores of Crohn's Disease Activity Index (CDAI), Pediatric Crohn's Disease Activity Index (PCDAI), and Lichtiger Colitis Activity Index (LCAI) (6)
3. Signs and symptoms
4. Date of initial diagnosis, and the latency period since first symptoms

Both at diagnosis and during the follow-up the following aspects were evaluated:

1. Disease extent (evaluated through gastrointestinal endoscopy and confirmed at histology on biopsies. The localisation of disease is indicated according to the Montreal classification (7))
2. Extraintestinal manifestations (muscular-skeletal, mucosal-skin, hepatic-biliary, ocular, pulmonary, genital-urinary, thrombotic-embolic, growth failure defined as height velocity/weight below the 5th percentile for age)
3. Perianal disease (diagnosis and scoring according to the Cardiff-Hughes classification for patients with CD (8,9))
4. Need for immunosuppressive therapy with steroids, thiopurines (azathioprine, 6-mercaptopurine), and/or anti-TNF-α (anti-tumour necrosis factor-α) and need to adjust treatment regimen during follow-up
5. Number and type of surgical procedures performed

During the follow-up, the number of severe relapses (defined by the clinical indexes PCDAI, CDAI, LCAI) and the stage of paediatric patients' development in height and weight were analysed.

Statistical Analysis

All of the data collected for each patient were then computerised using the Access database (Microsoft, Redmond, WA). A descriptive analysis was performed by investigating and comparing the onset and diagnosis of the disease and the follow-up of patients who developed IBD as children versus those who became ill in adulthood. The χ^2 and Student t tests were used to seek any significant differences between the 2 groups.

Kaplan-Meier survival analysis was applied to determine the cumulative incidence of surgical procedures, onset of perianal disease or extraintestinal complications, and outcome by age. Any statistically significant differences emerging between the curves were evaluated using the log-rank test.

Two multivariate analyses were undertaken to identify the predictive and characterising factors for the onset and follow-up of the disease in children versus adults. Both logistic regression analyses were conducted using the stepwise method (with entry significance level = 0.20 and stay significance level = 0.15). For each of the 2 logistic regression analyses, coefficients, odds ratios (OR), and the corresponding 95% confidence intervals (CIs), significance, and goodness of fit were calculated. $P < 0.05$ was considered significant. Both the descriptive and multivariate analysis were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Distribution of Patient Populations and Demographic Data

In all, 312 patients were evaluated; IBD had been diagnosed in 133 (42.6%) children (mean age at diagnosis 11.3 years; range 0–17 years) and in 179 (57.4%) adults (mean age at diagnosis 29.1 years; range 18–40 years) (Table 1). When the 133 paediatric-onset patients were divided according to their age at the time of diagnosis, 10 of them were 0 to 5 years old (2 with CD, 7 with UC, 1 with IBDU), 66 were 6 to 12 years old (34 with CD, 28 with UC, 4 with IBDU), and 57 were 13 to 18 years old (31 with CD, 23 with UC, 3 with IBDU).

Disease Onset

Latency Period

The mean age at onset was 10.5 years among the paediatric patients and 28.2 years among the adult cases; the mean interval between onset of symptoms and diagnosis of IBD (latency period) was 9 ± 16 months for the pediatric patients and 10.4 ± 19 months for the adult patients. In both groups, the mean latency periods were longer for patients with a diagnosis of CD or IBDU than for those with UC (Table 1).

Analysing the latency period among paediatric-onset patients in different age brackets showed that IBD was diagnosed within 15 months of the onset of symptoms in all the 0- to 5-year-olds, whereas it took more than 40 months to diagnose the condition in 5.7% of the children who were 6 to 12 years old at the time.

Onset Type and Severity

Table 2 compares the onset type (acute vs insidious) and severity (mild vs moderate or severe) of patients by type of diagnosis in the 2 groups. Moreover, it shows the percentages for signs, symptoms, and complications, indicated with the corresponding P values (where significant), for paediatric-onset and adult-onset patients at disease presentation, divided by type of diagnosis (Table 2). A delay in linear growth was recorded at disease onset in 37.2% of the children evaluated (23.5% with CD and 13.1% with UC).

Perianal Disease

Perianal disease was observed at disease onset in 17 (25.4%) paediatric patients with CD (50% of the 6- to 12-year-olds, 30.8% of the 13- to 17-year-olds, and 19.2% of the 0- to 5-year-olds) versus 8 (12.3%) adult patients ($P = 0.0001$).

Extraintestinal Manifestations

Extraintestinal manifestations at disease onset were observed in 19 (14.3%) paediatric patients and 13 (7.3%) adult patients ($P = 0.04$) (Table 2).

The most frequently observed extraintestinal manifestations among paediatric-onset cases were joint problems (4.1%: 5 patients with CD, 1 with UC), followed by oral aphthous lesions (2.8%: 2 patients with CD, 2 with UC), erythema nodosum (2.8%: 3 patients with CD, 1 with UC), and myalgia (2 patients with CD); secondary amenorrhoea and vulvar metastatic CD were observed in 1 case each.

Joint problems were also frequent among adult-onset patients (4.5% of patients, 6 with CD, 2 with UC), followed by deep venous thrombosis in 2 patients with UC. Erythema nodosum, osteopenia,

TABLE 1. Clinical characteristics of paediatric and adult patients at diagnosis

Variables	CD patients n = 132 (42.3)		UC patients n = 157 (50.3)		IBDU patients n = 23 (7.4)		Total n = 312 (100)	
	Ped n = 67 (50.8)	Ad n = 65 (49.2)	Ped n = 58 (36.9)	Ad n = 99 (63.1)	Ped n = 8 (34.7)	Ad n = 15 (65.2)	Ped n = 133 (42.6)	Ad n = 179 (57.4)
Sex								
Male/Female	1.03	1.5	0.71	1.48	7	1.14	0.96	1.45
Latency period								
Median, mo (range, min–max)	6 (0–105)	4 (0–88)	2 (0–78)	2 (0–135)	9 (2–15)	3 (1–79)	4 (0–105)	3 (0–135)
Average (mo)	11.3	12.4	6.6	9.2	8.1	9.3	9	10.4
Disease extent at diagnosis								
Upper gastrointestinal tract (L4)	28 (41.8)	10 (15.4)	—	—	2 (25.0)	1 (6.7)	30 (22.6)	11 (6.1)
Ileum (L1)	4 (6)	14 (21.5)	2 (3.4)	1 (1)				
Colon (L2)	13 (19.4)	16 (24.6)						
Ileum + colon (L3)	50 (74.6)	17 (26.2)						
Rectum (E1)			1 (1.7)	24 (24.2)				
Left colon (E2)			10 (17.3)	41 (41.4)				
Extended colitis (E3)			47 (81)	34 (34.3)				
Type of therapy at diagnosis								
Corticosteroids	24 (35.8)	22 (33.8)	25 (43.1)	23 (23.2)	2 (25)	1 (6.7)	51 (38.4)	46 (25.7)
Thiopurines	29 (43.3)	2 (3)	4 (6.9)	4 (4)	0	0	33 (24.8)	6 (3.4)
Anti-TNF-α	1 (1.5)	2 (3)	0	0	0	0	1 (0.8)	2 (1.1)

Disease extent at diagnosis according to Montreal classification. Ad = adult onset; CD = Crohn disease; IBDU = unclassified inflammatory bowel disease; Ped = paediatric onset; TNF-α = tumour necrosis factor-α; UC = ulcerative colitis.

TABLE 2. Disease related characteristics at onset in children and adults

Variables	CD patients n = 132 (42.3)		UC patients n = 157 (50.3)		IBDU patients n = 23 (7.4)		Total n = 312 (100)		
	Ped n = 67 (50.8)	Ad n = 65 (49.2)	Ped n = 58 (36.9)	Ad n = 99 (63.1)	Ped n = 8 (34.7)	Ad n = 15 (65.2)	Ped n = 133 (42.6)	Ad n = 179 (57.4)	*P*
Disease type									
Acute	37 (55.2)	40 (61.5)	48 (82.8)	54 (54.5)	5 (62.5)	10 (66.7)	90 (67.7)	104 (58.1)	NS
Insidious	30 (44.8)	25 (38.5)	10 (17.2)	45 (45.5)	3 (37.5)	5 (33.3)	43 (32.3)	75 (41.9)	NS
Severity									
Mild	13 (19.4)	10 (15.4)	17 (29.3)	35 (35.4)	6 (75)	6 (40)	36 (27.0)	51 (28.5)	NS
Moderate/severe	54 (80.6)	55 (84.6)	41 (70.7)	64 (64.6)	2 (25)	9 (60)	97 (73.0)	128 (71.5)	NS
Signs and symptoms									
Diarrhoea	12 (17.9)	24 (36.9)	21 (36.2)	36 (36.4)	2 (25)	6 (40)	35 (26.3)	66 (36.9)	0.05
Blood in stool	19 (14.3)	24 (36.9)	55 (41.4)	87 (87.9)	7 (5.2)	8 (53.3)	81 (60.9)	119 (66.5)	NS
Severe abdominal pain	29 (21.8)	53 (81.5)	24 (18)	42 (42.4)	3 (2.3)	6 (40)	56 (42.1)	101 (56.4)	0.008
Anorexia/nausea	23 (17.3)	51 (78.5)	14 (10.5)	49 (49.5)	0	5 (33.3)	37 (27.8)	105 (58.7)	<0.0001
Vomiting	10 (7.5)	2 (3)	3 (2.3)	3 (3)	0	0	13 (9.8)	5 (2.8)	0.009
Asthenia	29 (21.8)	44 (67.7)	31 (23.3)	36 (36.4)	3 (2.3)	5 (33.3)	63 (47.4)	85 (47.5)	NS
Fever	33 (24.9)	38 (58.5)	20 (15)	20 (20.2)	0	2 (13.3)	53 (39.9)	60 (33.5)	NS
Complications									
Surgery	4 (6)	7 (10.8)	0	1 (1)	0	0	4 (3.0)	8 (4.5)	NS
Perianal disease	17 (25.4)	8 (12.3)	—	—	—	—	17 (12.8)	8 (4.5)	<0.0001
Extraintestinal manifestations	14 (20.9)	9 (13.8)	5 (3.8)	4 (4)	0	0	19 (14.3)	13 (7.3)	0.05

P value reported when <0.05. Ad = adult onset; CD = Crohn disease; IBDU = unclassified inflammatory bowel disease; NS = not significant; Ped = paediatric onset; UC = ulcerative colitis.

TABLE 3. Logistic analysis: paediatric-onset IBD profile

	Coefficient	OR	CI	Significance
Intercept	0.093	—	—	0.76
Diagnosis				
IBDU	−0.46	0.76	0.259–2.242	0.21
CD	0.64	2.27	1.208–4.268	0.013
UC (ref)		1		
Insidious onset	−1.1	0.33	0.174–0.639	0.0009
Abdominal pain at onset				
Absent	0.123	2.44	1.086–5.485	0.62
Mild	0.65	4.12	2.022–8.406	0.003
Severe (ref)		1		
Anorexia/nausea	−1.8	0.17	0.087–0.311	<0.0001
Vomiting	2.1	7.95	2.179–28.967	0.002
Asthenia	0.74	2.1	1.087–4.050	0.027
Fever	0.48	1.62	0.851–3.081	0.14
Surgery	−1.28	0.28	0.061–1.277	0.1
Perianal disease	1.63	5.08	1.835–14.084	0.002
Extraintestinal manifestations	0.69	1.99	0.831–4.808	0.12

Concordance (concordant nodes) 79.0%; specificity 72.1% ($P = 0.5$); sensitivity 58.6% ($P = 0.5$); correctness (efficiency) 82.1% ($P = 0.5$). y = childhood onset ($P = 0.0001$). CD = Crohn disease; CI = confidence interval; IBD = inflammatory bowel disease; IBDU = unclassified inflammatory bowel disease; OR = odds ratio; UC = ulcerative colitis.

oral aphthous lesions, eye lesions, and pyoderma gangrenosum were seen in 1 patient each.

Analysis of Presenting Symptoms in IBD Developing in Different Paediatric Age Groups

Bloody diarrhoea was more common among the 0- to 5-year-old and 6- to 12-year-old children (92.3% and 64.3%, respectively) (OR 1.7; CI 0.83–3.46; $P = 0.146$).

Abdominal pain was severe in 40.3% of the 13- to 17-year-olds and 40% of the 6- to 12-year-olds, as opposed to 23.1% of the 0- to 5-year-olds.

Asthenia was more frequent among the 13- to 17-year-olds (43.8%) and the 6- to 12-year-olds (48.5%) than among the 0- to 5-year-olds (7.8%), and the same was true for fever (recorded in 52.8% of the 13- to 17-year-olds, 45.3% of the 6- to 12-year-olds, and 1.9% of the 0- to 5-year-olds).

A growth deficit was most common among the 6- to 12-year-old children (51.9% vs 42.6% of the 13- to 17-year-olds and 5.6% of the 0- to 5-year-olds), as was the presence of perianal disorders among patients with CD (found in 50% of the 6- to 12-year-olds vs 30.8% of the 13- to 17-year-olds and 19.2% of the 0- to 5-year-olds).

Extraintestinal manifestations were more frequent among the 6- to 12-year-olds (47.4%) and among the 13- to 17-year-olds (47.4%) than in the 0- to 5-year-olds (5.3%).

Logistic Analysis of Disease Onset

Paediatric-onset patients had CD more often than adult-onset patients ($P = 0.013$). Irrespective of the type of diagnosis, IBD of paediatric onset was less insidious ($P = 0.001$), with mild abdominal pain ($P = 0.003$), perianal disease ($P = 0.002$), and extraintestinal manifestations ($P = 0.1220$; OR 1.999). Among paediatric-onset patients, surgery was performed less frequently at disease onset ($P = 0.01$) (Table 3).

Diagnosis

Comparing the distribution of the 3 forms of IBD in the paediatric-onset versus adult-onset groups (Table 1), we found a greater prevalence of CD ($P = 0.045$) among paediatric-onset patients (50.4%) than among adult-onset cases (36.3%), whereas UC was more frequent (55.3%) among the paediatric-onset than among the adult-onset patients (43.6%).

In particular, among 10 (7.5%) children ages 0 to 5 years, 2 had a diagnosis of CD and 7 of UC. Among 66 (49.6%) 6 to 12 year-olds, 34 (51.5%) had a diagnosis of CD and 28 (42.4%) of UC. Among 57 (42.9%) children ages 13 to 17 years, there were 31 (54.4%) with a diagnosis of CD and 23 (40.4%) had UC.

Familiar Susceptibility

No significant differences were found between the paediatric and adult populations regarding familiarity for IBD or colon-rectum neoplasia. It was found in 21.2% of the adult patients versus 19.6% of the paediatric patients.

Disease Extent

Table 1 compares the site of disease at diagnosis in the 2 groups, by the type of diagnosis. The Montreal classification has been used as referral. In patients with *CD*, the disease was more frequently located in the upper gastrointestinal tract (L4) among paediatric-onset patients (41.8%) than among the adults (15.4%) ($P = 0.001$). An ileal localisation (L1) was seen in 6% of the paediatric patients and in 21.5% of the adults ($P = 0.009$). The ileal–colonic localisation (*L3*) was more frequently seen among the children (74.6%) ($P < 0.001$).

In cases with UC, extended colitis (E3) at diagnosis was more frequent among paediatric-onset patients (81%) than among the adults (34.3%) ($P < 0.0001$). An ulcerative proctitis (E1) was mostly observed among the adult patients (24.2%) than among the children (1.7%) ($P < 0.001$).

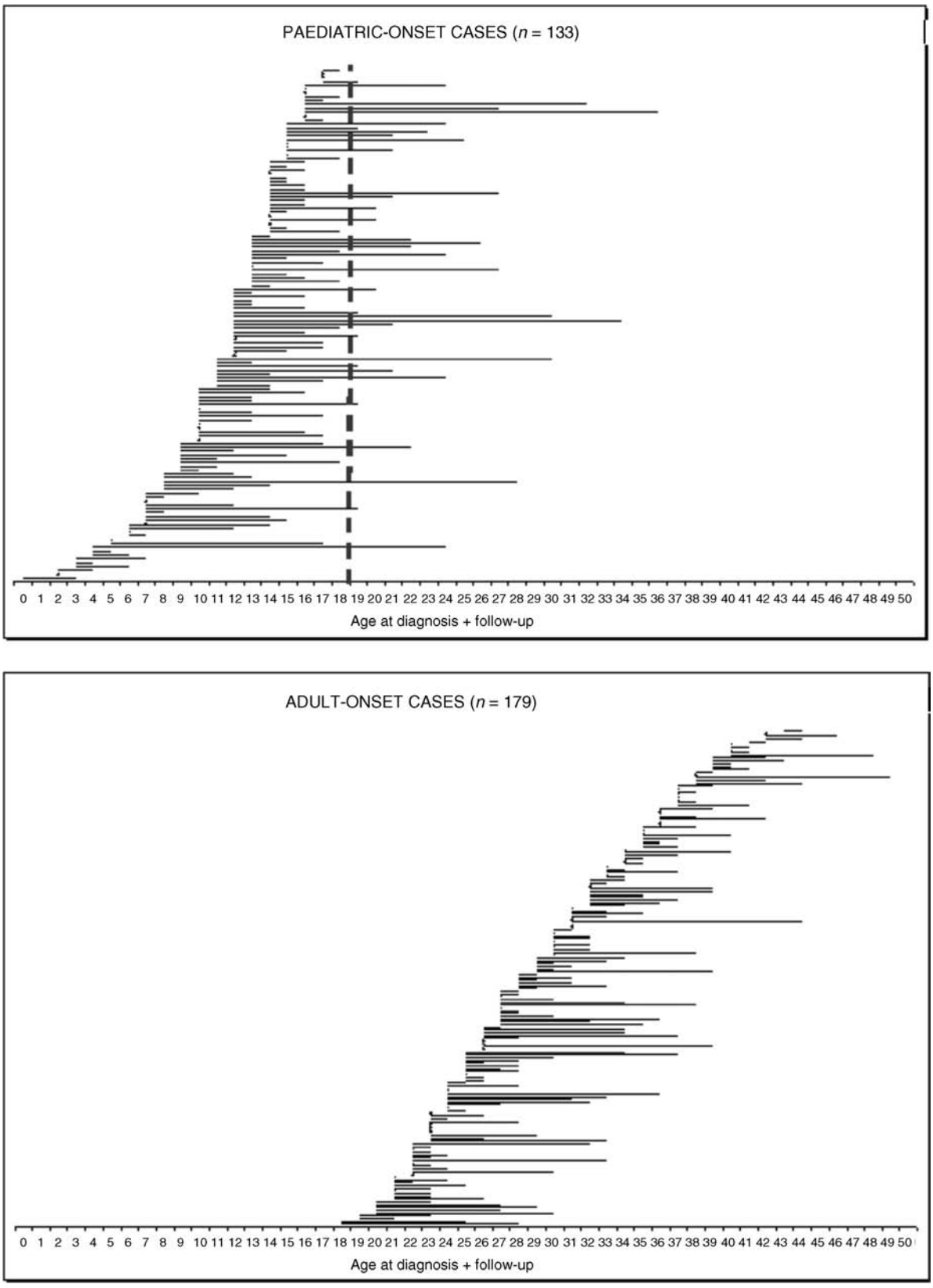

FIGURE 1. Follow-up data of each patient under study.

Analysis of Disease Extent Among the Different Paediatric Age Groups

Among the CD cases in paediatric-onset patients, upper gastrointestinal tract (L4) involvement was seen in 48.6% of the patients 6 to 12 years old and 36.4% of the 13- to 17-year-olds; the ileal site (L1 + L3) was affected in 80.0% of the patients 6 to 12 years old and 94% of the 13- to 17-year-olds. The colon (L2 + L3) was involved in all of the 0- to 5-year-old patients, in 94.3% of the 6- to 12-year-olds, and in 81.8% of the 13- to 17-year-olds.

Among the paediatric-onset cases of UC, no ileal involvement was observed in 0- to 5-year-old patients, whereas it was seen in 6.67% of the 6- to 12-year-olds and 4% of the 13- to 17-year-olds; a pancolic involvement (E3) was apparent in all the 0- to 5-year-olds, in 76.7% of the 6- to 12-year-olds, and in 64% of the 13- to 17-year-olds.

Follow-up

The mean follow-up was 4.8 years (63.9 months) for paediatric-onset patients and 3 years (36 months) for adult-onset patients (Fig. 1). Table 4 shows the changes in diagnosis during the follow-up, in the 2 groups of patients, by type of diagnosis.

Number of Severe Relapses

On comparing the 2 groups in terms of the number of severe relapses during the follow-up, paediatric-onset cases had a mean 2.1 episodes, as opposed to 1.7 in adult-onset cases. The number of episodes was ≤ 3 in 97% of adult-onset cases, whereas it was >3 in 9.5% of paediatric-onset patients.

A greater number of severe relapses occurred during the follow-up in the subgroup of paediatric-onset patients who had a growth deficiency at disease presentation than in those who did not (74.1% vs 25.9%).

Surgical Procedures

Comparable proportions of patients in the 2 groups required 1 or more surgical procedures during their follow-up (13% and 14%, respectively). Table 4 shows the percentages of patients operated on in the 2 groups, divided by type of diagnosis.

Among paediatric-onset patients, 7 had colectomy (3 CD and 4 UC) and 13 had small and/or large bowel resections; among the adults, 2 had colectomy (2 CD) and 15 had small and/or large bowel resections. Three paediatric-onset patients had 3 or more surgical procedures, whereas none of the adults had more than 2 operations.

Comparing the 2 groups at same time in follow-up, that is, after 3 years since their date of diagnosis, 1 or more surgical procedures had been performed in 9 (13.4%) paediatric-onset patients with CD versus 17 (26.1%) adult-onset patients with CD ($P = 0.0062$), as well as in 2 paediatric-onset patients with UC and 1 adult patient with UC.

We also considered those patients having >3 severe relapses and/or ≥ 1 surgical procedures during the follow-up: these were 14 (20.9%) paediatric-onset patients with CD versus 22 (33.8%) adult-onset patients with CD ($P = 0.012$), as well as 2 paediatric patients with UC versus 4 adult-onset patients with UC.

Perianal Disease

Perianal disease was observed in 30 paediatric-onset patients with CD (44.8%) and in 14 (21.5%) adult-onset patients with CD ($P = 0.006$) (Fig. 2).

TABLE 4. Clinical course of the paediatric and adult patients

Variables	CD patients n = 132 (42.3)		UC patients n = 157 (50.3)		IBDU patients n = 23 (7.4)		Total n = 312 (100)		P
	Ped n = 67 (50.8)	Ad n = 65 (49.2)	Ped n = 58 (36.9)	Ad n = 99 (63.1)	Ped n = 8 (34.7)	Ad n = 15 (65.2)	Ped n = 133 (42.6)	Ad n = 179 (57.4)	
Mean no. severe relapses, and range (min–max)	2.3 (1–7)	1.7 (1–4)	1.8 (1–5)	1.6 (1–6)	2 (1–4)	1.8 (1–3)	2.1 (1–7)	1.7 (1–6)	
Surgical procedures/resections	14 (20.9)	21 (32.3)	3 (5.2)	2 (2.0)	—	2 (13.0)	17 (12.8)	25 (14.0)	
Perianal disease	30 (44.8)	14 (21.5)	—	—	—	—	30 (44.8)	14 (21.5)	0.006
Extraintestinal manifestations	38 (56.7)	28 (43.1)	27 (46.6)	31 (31.3)	2 (25)	3 (20)	67 (50.4)	62 (34.6)	0.005
Changes in diagnosis to									
IBDU	—	—	—	—	6 (75.0)	12 (80.0)	—	—	
CD	67 (100.0)	65 (100.0)	6 (10.3)	2 (2)	1 (12.5)	2 (13.3)	7 (5.3)	4 (2.2)	
UC	—	—	52 (89.7)	97 (98)	1 (12.5)	1 (6.7)	1 (0.8)	1 (0.6)	
Therapy (during follow-up)									
Corticosteroids	48 (71.6)	39 (60)	37 (63.8)	43 (43.4)	2 (25)	3 (20)	87 (65)	85 (47.5)	0.003
Thiopurines	45 (67.2)	20 (30.8)	21 (36.2)	18 (18.2)	0	0	66 (49.6)	38 (21.2)	<0.0001
Anti-TNF-α	14 (20.9)	10 (15.4)	5 (8.6)	1 (1)	0	0	19 (14.3)	11 (6.2)	0.016

Ad = adult onset; CD = Crohn disease; IBDU = unclassified inflammatory bowel disease; Ped = paediatric onset; TNF-α = tumour necrosis factor-α; UC = ulcerative colitis.

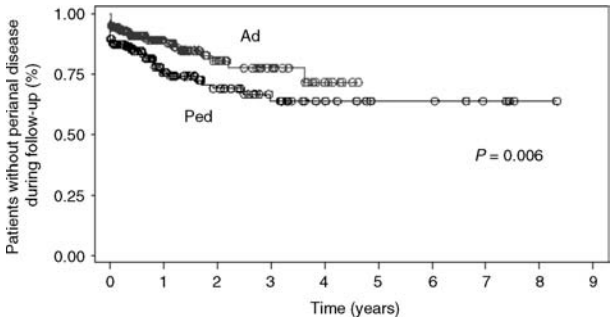

FIGURE 2. Occurrence of perianal diseases during the follow-up paediatric-onset (Ped) and adult-onset (Ad) cases.

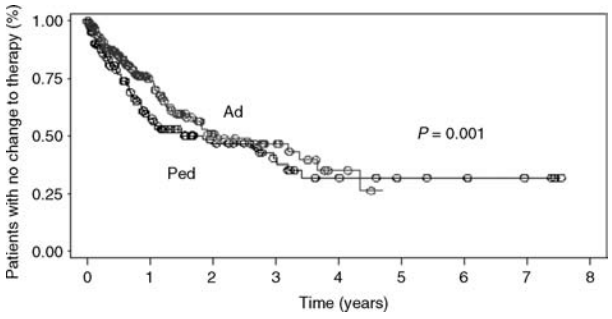

FIGURE 3. Need to step-up therapy in paediatric-onset (Ped) and adult-onset (Ad) patients during the follow-up.

Extraintestinal Manifestations

Extraintestinal manifestations were observed during the follow-up in 50.4% of patients with paediatric onset and 34.6% of the patients with adult onset ($P = 0.005$). Table 4 shows the extraintestinal manifestations identified during follow-up in the 2 groups, divided by type of IBD diagnosis. Considering the separate age brackets in the paediatric-onset group, extraintestinal manifestations came to light during the follow-up in 58.5% of the 6- to 12-year-olds versus 32.3% of the 13- to 17-year-olds ($P = 0.002$).

Therapeutic Management at Diagnosis and During Follow-up

Therapy at Diagnosis

Table 1 shows the type of therapy administered at diagnosis in the 2 groups, divided by type of disease. No statistically significant difference emerged between the 2 groups regarding the use of anti-TNF-α drugs at diagnosis (0.8% of paediatric-onset patients and 1.1% of the adults).

Among paediatric-onset patients, the age bracket most often given anti-TNF-α therapy at diagnosis was the 6- to 12-year-old patients with CD (53.3% vs 40% of 13- to 17-year-olds and 6.7% of 0- to 5-year-olds).

An exclusive polymer diet was administered for 6 to 8 weeks after diagnosis in 40% of 6- to 12-year-old patients with CD and 18.2% of 13- to 17-year-old patients with CD.

Therapy During Follow-up

Anti-TNF-α drugs were needed for 14.3% of the paediatric-onset patients and 6.2% of the adults ($P = 0.016$). Among the pediatric patients, these drugs were administered to 16.7% of the 0- to 5-year-olds, 21.6% of the 6- to 12-year-olds, and 17.7% of the 13- to 17-year-olds (Table 4). Among the adult-onset patients, cases of CD were more often treated with anti-TNF-α therapy (15.4%) than those with UC or IBDU ($P = 0.002$) (Fig. 3).

Logistic Analysis of Disease Diagnosis and Follow-up

Irrespective of the type of diagnosis, more paediatric-onset patients required thiopurines ($P < 0.0001$) or corticosteroids ($P = 0.01$) at the time of their diagnosis, and their scheduled therapy changed during the follow-up more frequently than it did among the adult-onset patients ($P = 0.04$) (Table 5).

DISCUSSION

Epidemiological studies show that IBD can develop at any age, the incidence of CD peaking in late adolescence or early adulthood and that of UC at 10 to 18 years of age (1,10,11). Diagnosis in infancy or childhood occurs in 15% to 20% of cases, and there has been a significant increase in the incidence of the 3 forms of IBD in young people in the last 2 decades (12,13).

A diagnosis of CD is more common in paediatric-onset patients with IBD; the preferential disease location of CD is at

TABLE 5. Logistic analysis: IBD profile of childhood-onset follow-up

	Coefficient	OR	CI	Significance
Intercept	−0.85	—	—	0.0003
Diagnosis				
IBDU	0.1	1.5	0.572–3.942	0.75
CD	0.2	1.66	0.967–2.850	0.35
UC (ref)		1		
Corticosteroids at diagnosis	0.74	2.1	1.182–3.749	0.0114
Immunosuppressants at diagnosis	2.26	9.55	3.698–24.643	<0.0001
Changes to therapy during follow-up	0.54	1.71	1.024–2.868	0.04
Associated diseases during follow-up	0.89	2.43	1.406–4.189	0.002

Concordance (concordant nodes) 71.7%; specificity 65.1% ($P = 0.5$); sensitivity 45.1% ($P = 0.5$); correctness (efficiency) 79.9% ($P = 0.5$). y = childhood onset ($P = 0.0001$). CD = Crohn disease; CI = confidence interval; IBD = inflammatory bowel disease; IBDU = unclassified inflammatory bowel disease; OR = odds ratio; UC = ulcerative colitis.

the ileocolic region and in the upper gastrointestinal tract, whereas UC is often localised at the extended colon (14–18). Growth failure is common in paediatric CD patients (60%), as is the simultaneous occurrence of extraintestinal manifestations (7%–24%) (19,20).

The present study aimed to ascertain whether any significant phenotypic differences exist between patients with IBD whose disease developed in paediatric age or as adults diagnosed and studied during a defined period of time.

In our study, all of the paediatric and adult patients enrolled had received a diagnosis of IBD within the same time interval (1994–2008), allowing a limitation of possible biases due to different technologies or instrumentation being available.

Significant differences emerged between the 2 groups in terms of signs, symptoms, and complications. At disease onset, the classic symptoms of IBD (ie, severe abdominal pain, diarrhoea) were observed more frequently in adult-onset patients than in paediatric-onset cases, and more of the adult-onset patients needed surgery at disease presentation. Perianal disease, extraintestinal manifestations, and associated diseases were more frequent at the onset of IBD among paediatric-onset patients than among the adult-onset patients. The clinical presentation of IBD is less typical when it first develops in childhood than in adult age, so it is less likely to be suspected; 40.6% of our paediatric-onset patients had a growth deficiency at disease presentation, and the ratio of extraintestinal signs (particularly joint problems) between the paediatric- and the adult-onset cases was 2:1. These findings are consistent with the more exhaustive data available in the Italian Registry of Paediatric IBD (our paediatric-onset patients are also included in the Italian Registry, so we were able to compare our cases seen at the Department of Paediatrics of Padua with the whole population of children in the National Registry) (14). Several authors have reported such diversity between patients with paediatric- and adult-onset IBD as regards the baseline clinical features (12,20,21).

Within the group of patients with paediatric-onset IBD, the phenotypic expression of the disease appeared to vary in different age brackets, as reported by other authors (5). Considering the features of the disease at its onset and the site of disease at its diagnosis, the 13- to 17-year-olds more closely resembled the situation seen in adult-onset patients (with severe abdominal pain and needing surgery), whereas the phenotype of IBD in the younger children ($\leq$12 years old) was characterised by vomiting, asthenia, growth deficiency, and perianal disease at onset, and involvement of the upper gastrointestinal tract among patients with CD when IBD was diagnosed.

The mean latency period (from the onset of symptoms to the diagnosis) was shorter in our paediatric-onset patients (9 months) than in the adult-onset group (10.4 months). The main factors influencing the chances of early diagnosis are the specificity and intensity of the symptoms at the onset of the disease. A possible explanation for our findings may be that although children tend more frequently to have nonspecific systemic symptoms (rather than the typical IBD symptoms often observed in cases of IBD developing in adults), the effect of these early manifestations on the child's health, and consequently on the family, is usually stronger than in adults developing IBD, so medical care is sought earlier for children (who are also monitored more closely than adults by our public health system).

In agreement with findings in the literature (15), our results show that the latency period is significantly longer for patients with CD or IBDU than for patients with UC, whatever the age of onset of the disease, reflecting a different diagnostic immediacy for the 3 different forms of IBD.

The initial diagnosis was IBDU in 6% of our paediatric-onset patients and 8.4% of those in the adult-onset group. Among these patients with IBDU, subsequent changes to the diagnosis of UC and CD occurred more frequently during follow-up in both groups. This observation may support the conviction that IBDU is not a separate form of IBD requiring independent classification, but is a phenotypically undefined phase of CD or UC (22).

Among our patients, the inflammatory CD phenotype was more common in the paediatric-onset group, whereas stricturing and penetrating phenotypes were seen more often in the adult-onset group. Although the differences were not statistically significant, they are consistent with other reports; because the stricturing and penetrating phenotypes appear as the disease evolves, they occur later in the follow-up (12). A recent study by Van Limbergen et al (3) showed that the pattern of childhood-onset CD progresses significantly from diagnosis up to a 4-year follow-up, with an increase in stricturing and penetrating disease (from 4.4% to 12.9% and from 4.4% to 11.4%, respectively) and a decrease in the inflammatory phenotype (from 91.2% to 75.8%).

CD in the upper digestive tract was more common among our paediatric-onset cases than among the adult-onset ones (Table 1), as in the sample described by Van Limbergen et al (3), who found that more than half of the children they investigated had CD proximal to the terminal ileum at diagnosis. The reliability of this observation may experience partially a bias; however, unlike the situation in adults, upper gastrointestinal tract endoscopies are routinely performed in paediatric patients to establish the diagnosis and ascertain the stage of the disease because the symptoms are often nonspecific in this age group. The evidence of a more frequent ileocolic localisation for children with CD and extended colitis for children with UC in our population also corresponded with what Van Limbergen's sample described.

As for the treatment of the 2 groups, steroids were given significantly more often to children, even though the effects of such drugs on bone health and growth processes should induce paediatricians to limit their use (23). It must be said, however, that children are only given steroids in cases of severe relapse, rapidly tapering off the doses within a few weeks and subsequent switching to dietary measures. Each steroid cycle administered to a given patient was counted to compare the therapeutic management of our 2 groups. Concerning the anti-TNF-α treatment with infliximab, in Italy this has been widely used in gastroenterology since the early 2000s for adult patients, whereas in this same period it was less commonly used for children (only as an off-label drug and with previous informed consent). The official indication for paediatric age dates to March 2007. Such a dishomogeneity between the 2 groups compared may reduce the validity of the results described.

Our direct comparison between the phenotypic features of IBD acquired in childhood or adulthood showed that younger patients with CD more often have disease in the ileocolic region and upper digestive tract, and tend to develop perianal disease and extraintestinal manifestations more frequently during follow-up, and need to change their scheduled therapy.

In patients with UC, the site of disease is more frequently pancolitis when the disease develops in childhood instead of the rectal-sigmoid site that is typical in adults. Paediatric-onset patients more frequently must change the scheduled therapy during follow-up. A change of diagnosis from UC to CD is also seen more often among paediatric-onset cases than in those developing the disease in adult life.

Our effort to dichotomise the disease course as favourable or unfavourable, according to the number of severe relapses and/or surgical procedures during follow-up, did not confirm the common clinical impression of a more severe disease presentation and course among IBD cases with paediatric onset. Rather, we had strong evidence of a different disease phenotype according to the age of disease onset.

The phenotypic and clinical differences between our 2 groups may have been due to different mucosal immunological defences, which are incompletely developed in paediatric age. Whatever the clinical manifestations of IBD, the immunopathogenic mechanisms underlying the disease change considerably through the years and this may explain why immunomodulating drugs that are effective in the early stages of the disease may no longer be helpful in the long term. In children who develop IBD, treating the disease as soon as it comes to light may permit modification of the disease's natural history, whereas this would be more difficult to achieve in adult patients with a long-standing history of disease (24).

CONCLUSIONS

In our study, the phenotypic expression of IBD differed between patients who developed the disease as children or as adults as regards both the onset of the disease and its follow-up. Irrespective of the type of diagnosis, the onset and follow-up of patients becoming ill in paediatric age are more frequently characterised by perianal disorders and extraintestinal manifestations.

This diversity may have important practical implications; the approach to these patients should be age related and the transition from childhood to adulthood warrants particular attention, demanding a direct collaboration between paediatric and adult gastroenterologists when it comes to transferring adolescents with IBD from paediatric to adult care providers. Further studies are needed to clarify the numerous clinical aspects of early- and late-onset IBD and this calls for cooperation between paediatric and adult gastroenterologists to ameliorate the data collection in this field (25,26).

REFERENCES

1. Farrokhyar F, Jan Irvine E, Swarbrick ET. A critical review of epidemiological studies in inflammatory bowel disease. *Scand J Gastroenterol* 2001;1:2–15.
2. Griffiths AM, Hugot JP. Crohn's disease. In: Walker WA, Goulet O, Kleinman RE, et al, eds. *Pediatric Gastrointestinal Disease*. 4th ed. Hamilton, Canada: B.C. Decker; 2004; 789–824.
3. Van Limbergen J, Russel RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114–22.
4. Freeman JH. Comparison of longstanding pediatric-onset and adult-onset Crohn's disease. *J Paediatr Gastroenterol Nutr* 2004; 39:183–6.
5. Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;146:35–40.
6. Noble A, Turner D. Clinical indices for pediatric inflammatory bowel disease research. In: Mamula P, Markowitz JE, Baldassano RN, eds. *Pediatric Inflammatory Bowel Disease.* New York: Springer; 2008: 507–30.
7. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749–53.
8. Sandborn WJ, Fazio VW, Feagan BG, et al. American Gastroenterological Association Clinical Practice Committee. Technical review of perianal Crohn's disease. *Gastroenterology* 2003;125:1508–30.
9. Hughes LE. Clinical classification of perianal Crohn's disease. *Dis Colon Rectum* 1992;5:928–32.
10. Corraro G, Miglio F, Tragnone A, et al. Incidence of IBD in Italy: a nationwide population-based study–Gruppo Italiano per lo Studio del Colon e Retto (GISC). *Int J Epidemiol* 1997;26:904–6.
11. Molinié F, Gower-Rousseau C, Yzet T, et al. Opposite evolutions in the incidence of Crohn's disease and ulcerative colitis in Northern France (1988–1999). *Gut* 2004;53:843–8.
12. Nieuwenhuis ES, Escher JC. Early onset IBD: what's the difference? *Dig Liv Dis* 2008;40:12–5.
13. Mesquita MB, Civitelli F, Levine A. Epidemiology, genes and inflammatory bowel diseases in childhood. *Dig Liv Dis* 2008;40:3–11.
14. Castro M. Inflammatory bowel disease in children and adolescents in Italy: data from the Pediatric National IBD Register (1996–2003). *Inflamm Bowel Dis* 2008;14:1246–52.
15. Moyer MS. A collaborative effort to define the epidemiology of pediatric inflammatory bowel disease: what can we learn from children with early-onset disease? *J Pediatr* 2005;146:7–8.
16. Oliva-Hemker M, Fiocchi C. Etiopathogenesis of inflammatory bowel disease: the importance of the pediatric perspective. *Inflamm Bowel Dis* 2002;8:112–28.
17. Newby EA, Croft NM, Green M, et al. Natural history of paediatric inflammatory bowel diseases over a 5-year follow-up: a retrospective review of data from the register of paediatric inflammatory bowel diseases. *J Pediatr Gastroenterol Nutr* 2008;46:539–45.
18. Kugathasan S, Cohen S. Searching for new clues in inflammatory bowel disease: tell tales from paediatric IBD natural history studies. *Gastroenterology* 2008;135:1038–41.
19. Freeman HJ. Natural history and clinical behaviour of Crohn's disease extending beyond two decades. *J Clin Gastroenterol* 2003;37:216–9.
20. Bousvaros A. Common errors in the management of children with IBD. First International Symposium on Pediatric IBD. *J Pediatr Gastroenterol Nutr* 2006;43(Suppl 2):1–43.
21. Merchant A. Inflammatory bowel disease in children: an overview for pediatric healthcare providers. *Gastroenterol Nurs* 2007;30:278–82.
22. Odze RD. Pathology of indeterminate colitis. *J Clin Gastroenterol* 2004;38(Suppl 5):36–40.
23. Escher JC. Corticosteroid therapy. In: Mamula P, Markowitz JE, Baldassano RN, eds. *Pediatric Inflammatory Bowel Disease.* New York: Springer; 2008:363–8.
24. Faubion WA, Fiocchi C. Gut immunity and inflammatory bowel disease. In: Mamula P, Markowitz JE, Baldassano RN, eds. *Pediatric Inflammatory Bowel Disease.* New York: Springer; 2008:15–29.
25. Hait EJ, Barendse RM, Arnold JH, et al. Transition of adolescents with inflammatory bowel disease from paediatric to adult care: a survey of adult gastroenterologists. *J Paediatr Gastroenterol Nutr* 2008;48:61–5.
26. Hait EJ, Arnolg JH, Sands BE, et al. Transition to adult care. In: Walker-Smith JA, Lebenthal E, Branski D, eds. *Pediatric Inflammatory Bowel Disease: Perspective and Consequences.* Basel, Switzerland: Karger; 2009:191–8.