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See Dubinsky MC et al on page 1105 in *CGH*; See editorial on page 1038.

Background & Aims: **Childhood-onset inflammatory bowel disease (IBD) might be etiologically different from adult-onset IBD. We analyzed disease phenotypes and progression of childhood-onset disease and compared them with characteristics of adult-onset disease in patients in Scotland.** ***Methods:*** **Anatomic locations and behaviors were assessed in 416 patients with childhood-onset (276 Crohn's disease [CD], 99 ulcerative colitis [UC], 41 IBD type unclassified [IBDU] diagnosed before seventeenth birthday) and 1297 patients with adult-onset (596 CD, 701 UC) IBD using the Montreal classification.** ***Results:*** **At the time of diagnosis in children, CD involved small bowel and colon (L3) in 51% (138/273), colon (L2) in 36%, and ileum (L1) in 6%; the upper gastrointestinal (GI) tract (L4) was also affected in 51%. In 39%, the anatomic extent increased within 2 years. Behavioral characteristics progressed; 24% of children developed stricturing or penetrating complications within 4 years (vs 9% at diagnosis; $P < .0001$; odds ratio [OR], 3.32; 95% confidence interval [CI], 1.86–5.92). Compared with adults, childhood-onset disease was characterized by a "panenteric" phenotype (ileocolonic plus upper GI [L3+L4]; 43% vs 3%; $P < .0001$; OR, 23.36; 95% CI, 13.45–40.59) with less isolated ileal (L1; 2% vs 31%; $P < .0001$; OR, 0.06; 95% CI, 0.03–0.12) or colonic disease (L2; 15% vs 36%; $P < .0001$; OR, 0.31; 95% CI, 0.21–0.46). UC was extensive in 82% of the children at diagnosis, versus 48% of adults ($P < .0001$; OR, 5.08; 95% CI, 2.73–9.45); 46% of the children progressed to develop extensive colitis during follow-up. Forty-six percent of children with CD and 35% with UC required immunomodulatory therapy within 12 months of diagnosis. The median time to first surgery was longer in childhood-onset than adult-onset patients with CD (13.7 vs 7.8 years; $P < .001$); the reverse was true for UC.** ***Conclusions:*** **Childhood-onset IBD is characterized by extensive intestinal involvement and rapid early progression.**

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are complex polygenic diseases, and are a major cause of morbidity in Europe and North America, where up to 1 in 250 of the general population are affected.[1] The direct economic costs are estimated as £720 million per year for patients in the United Kingdom.[1,2]

As many as 25% of patients first present during childhood or adolescence.[3] In children, these diseases have been marked by a steady rise in incidence over the last 4 decades, with disease presenting most commonly immediately before the start of the teenage years, thereby impacting on emotional and physical development as well as affecting linear growth, education, and future employment prospects.[4]

It has remained a topic of great debate whether childhood-onset disease is etiologically distinct from adult-onset disease—a debate recently catalyzed by the search for susceptibility genes in CD and UC. Clinical experience, including the early requirement for second-line immunomodulatory drugs[5,6] in childhood-onset disease, suggests that childhood-onset disease may have a more "severe" phenotype. This hypothesis has been supported to some extent by the limited available data suggesting that childhood-onset CD may be characterized by extensive intestinal involvement at presentation.[7–9] However, rigorous studies investigating the progression of intestinal involvement and behavior in childhood disease are not available to help explore this hypothesis further.

Abbreviations used in this paper: CI, confidence interval; IBDU, inflammatory bowel disease type unclassified; OR, odds ratio.

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Table 1. Demographics of IBD Patients With Childhood-Onset[a] and Adult-Onset[b] Inflammatory Bowel Disease

Childhood IBD (n = 416)	CD	UC	IBDU
N	276	99	41
Male/female	164/112	48/51	19/22
Median age at diagnosis (*y*) (Q1–Q3)	11.5 (8.9–13.2)	10.9 (8.8–10.8)	10 (7.6–12.5)
Caucasian	97.8% (270/276)	94.9% (94/99)	97.5% (40/41)
Median duration of follow-up (*y*) (Q1–Q3)	3.7 (1.7–6.0)	3.5 (1.1–4.8)	2.5 (0.4–4.1)
Smoking at diagnosis (all IBD) (yes/no/ex-smoker)		1.6%/95.3%/3.1%	
Adult IBD (n = 1297)	CD		UC
n	596		701
Male/female	216/380		342/359
Median age at diagnosis (*y*) (Q1–Q3)	29.7 (23.7–43.5)		34.5 (26.0–50.0)
Caucasian	99.3% (578/582)		97.3% (673/688)
Median duration of follow-up (y) (Q1–Q3)	10.3 (3.8–20.6)		8.9 (4.2–16.5)
Smoking at diagnosis (yes/no/ex-smoker)	43.9%/44.4%/11.7%		19.2%/49.9%/30.9%

IBDU, IBD type unclassified.
[a]Age <17 years at diagnosis; Montreal A1.
[b]Age >17 years at diagnosis; Montreal A2–A3.

In contrast with childhood-onset disease, the development of internationally accepted disease classification systems in recent years has facilitated longitudinal studies addressing changes in disease phenotype in adults with IBD.[10] A series of careful studies have consistently demonstrated the stability of disease location over time, as well as the progression of the behavior phenotype from purely inflammatory disease to either stricturing or penetrating disease.[11] The most recent classification system, proposed by the Montreal working party, attempted to integrate the increasing knowledge basis that had evolved since previous groups in Rome and Vienna had addressed these issues.[12] Although best considered a work in progress, the Montreal classification has formed the basis of phenotypic classification in many published adult clinical and genetic studies since 2005.

In the present study, we have described the presenting phenotype and progression of disease phenotype in childhood-onset CD and UC. We have used the phenotypic subclassification system for disease behavior and location suggested in the report of the Montreal working party,[12] and we have used the age of ≤16 years at diagnosis to define childhood-onset disease (A1 in the Montreal classification). We also studied the phenotype of IBD in the subgroup of children diagnosed in early childhood—before the eighth birthday. We evaluated the need for immunosuppressive medication and surgery in childhood-onset disease, and compared time to first surgery in childhood-onset and adult-onset IBD. Finally, we assessed whether the phenotype of childhood-onset IBD may be different from adult-onset IBD by comparing these phenotypic characteristics in the Scottish population.

Methods

Subjects

We recruited 416 children with IBD diagnosed before their seventeenth birthday from all the pediatric gastroenterology centers in Scotland as part of an ongoing childhood-onset IBD genetics project from July 2002. Children were investigated according to the ESPGHAN "Porto"-criteria for diagnosis of IBD.[13,14] Detailed patient demographics are presented in Table 1. We also recruited 1297 patients with adult-onset IBD from the Gastroenterology Department at Western General Hospital, Edinburgh from January 2000 as part of an ongoing IBD genetics project. Detailed demographics are presented in Table 1.

The study was approved by the local Research Ethics Committee. Informed personal or parental consent was obtained.

Classification of IBD

The diagnosis of IBD was based on standard criteria as set out by Lennard–Jones.[15] All patients were phenotyped using the Montreal classification (Table 2), which has addressed some of the difficulties of previous systems in classifying pediatric IBD: a childhood-onset category was introduced (<17 years at diagnosis) and the Vienna classification was modified so that upper gastrointestinal (GI) disease could "coexist" with lower GI locations of disease.[12,16] A dedicated database manager (H.E.D.) performed quality control of phenotypic data entered onto a Microsoft Access database (Microsoft Corporation, Redmond, WA). Oral CD was defined by macroscopic/biopsy changes after examination by a pediatric dentist/oral medicine specialist only.

We scored the progression of anatomic involvement of the GI tract and disease behavior in 2-yearly intervals to 4 years in childhood-onset CD. Adult-onset CD location was assessed at last clinical follow-up and adult-onset CD behavior was analyzed after 5 years clinical follow-up. Childhood-onset and adult-onset UC were assessed at diagnosis and at last clinical follow-up. When comparing childhood-onset and adult-

Table 2. The Montreal Classification of Crohn's Disease

Age at diagnosis (*y*)			
A1	≤16		
A2	17–40		
A3	>40		
CD location			
L1	Terminal Ileum (TI)	L1 + L4	TI + upper GI
L2	Colon	L2 + L4	Colon + upper GI
L3	Ileocolon	L3 + L4	Ileocolon + upper GI
L4	Upper GI		
CD behavior			
B1	Nonstricturing, nonpenetrating	B1p	Nonstricturing, nonpenetrating + perianal
B2	Stricturing	B2p	Stricturing + Perianal
B3	Penetrating	B3p	Penetrating + Perianal
UC: Disease extent			
E1	Proctitis		
E2	Left sided (distal)		
E3	Extensive (pancolitis)		

onset IBD, the location was defined as the maximum extent by the time of last follow-up but before the first resection.[12]

In addition to the 4 disease locations described in the Vienna classification (ileal, colonic, ileocolonic, and upper GI [L1–L4]) the Montreal classification added 3 further subcategories; these were the first 3 categories (L1–L3) with the addition of L4 where the disease sites coexisted, meaning the L4 disease location no longer negated the presence of often substantial lower GI disease allowing for more in-depth phenotypic analysis.[16] Recognition was given to the fact that enteric and perianal fistulae may represent different disease phenotypes. Thus, perianal disease was removed from the B3 category and instead added as a suffix "p" to any of the disease categories, B1–B3.

In patients with UC disease, extent was divided into 3 categories: E1 for patients with a proctitis (inflammation limited to the rectum); E2 for left-sided disease distal to the splenic flexure; and E3 for extensive disease proximal to the splenic flexure.

Statistical Analysis

To avoid statistical errors generated by multiple testing, we opted to analyze our data first as contingency tables consisting of columns of Montreal categories versus rows of different time points of clinical follow-up. After this, unifactorial analyses were performed using χ^2 or Fisher's exact test (when $n < 5$ per field of 2×2 table) to calculate odds ratios (OR) and 95% confidence intervals (CI). Minitab software (Release 13.20; Minitab Inc, State College, PA) and GraphPad Instat software (v 3.06; San Diego, CA) were used. Kaplan–Meier curves to assess time from diagnosis to first surgical resection were calculated using GraphPad Prism software (v 4.0). Analysis of time to use of immunomodulatory drug therapy (first use of any of azathioprine, methotrexate, or biological therapy) was also assessed and is presented as a Kaplan–Meier curve in the childhood-onset group only. Differences between Kaplan–Meier curves were compared using a log-rank test automatically calculated in Prism.

Results

Phenotypic Characteristics of Childhood-Onset CD

CD at diagnosis. CD affected the small as well as large bowel (L3 ± L4) in 50.5%, the colon (L2 ± L4) in 36.3%, and the ileum (L1 ± L4) in 5.9%. More than half of children (50.9%) were affected by CD proximal to the terminal ileum at diagnosis (any L4). Follow-up of ≥2 years was completed for 196 of 273 patients (71.8%). Follow-up data of ≥4 years were available for 132 of 273 patients (48.4%; Table 3).

CD location. The location of disease changed over time. Detailed analysis of the 196 childhood-onset CD patients who had ≥2 years follow-up demonstrated that a large proportion of these children experienced extension of anatomic involvement of the GI tract. At diagnosis, 53 of 196 (27.0%) already had the maximum disease extent (L3 + L4). Of the 143 children who could therefore change CD location at 2 years follow-up, 56 (39.1%) children did. These changes were due to the inclusion of findings on upper GI endoscopy in 15 of 56 (26.8%) only; in the majority (41/56, 73.2%), changes were due to extension from localized disease to more extensive disease involving the lower GI tract. This extension of anatomic involvement was more likely to be due to increasing ileal involvement over time (27/56 [48.2%] patients [ileal, 23; ileocolonic, 4]) rather than colonic involvement with time (11/56 [19.6%]; $P = .001$; OR, 3.81; 95% CI, 1.64–8.84).

CD behavior. Disease behavior progressed significantly from diagnosis to 4 years follow-up ($P = .001$). By 2 years follow-up, the behavior of CD changed with an increase in stricturing disease (±perianal) from 4.4% to

Table 3. Comparison of Montreal Disease Location and Behavior at Diagnosis, at Follow-Up of ≥2 Years and Follow-Up of ≥4 Years in Childhood-Onset CD Patients

Childhood-onset CD	At diagnosis, *n* (%) (*N* = 273)	At follow-up ≥2 years, *n* (%) (*N* = 196)	At follow-up ≥4 years, *n* (%) (*N* = 132)
CD phenotype: Location*			
L1	10 (3.7)	5 (2.6)	4 (3.0)
L2	57 (20.9)	30 (15.3)	24 (18.2)
L3	53 (19.4)	32 (16.3)	20 (15.2)
L1 + L4	6 (2.2)	4 (2.0)	3 (2.3)
L2 + L4	42 (15.4)	32 (16.3)	24 (18.2)
L3 + L4	85 (31.1)	86 (43.9)	51 (38.6)
L4	6 (2.2)	2 (1.0)	2 (1.5)
P		.61	
CD phenotype: Behavior			
B1 (±p)	215 (no p) (78.8)	136/197 (69.0)	81 (61.4)
	249 (±p) (91.2)	163/197 (82.7)	100 (75.8)
B2 (±p)	9 (no p) (3.3)	14/197 (7.1)	10 (7.6)
	12 (±p) (4.4)	19/197 (9.6)	17 (12.9)
B3 (±p)	11 (no p) (4.0)	14/197 (7.1)	12 (9.1)
	12 (±p) (4.4)	15/197 (7.6)	15 (11.4)
P		.001	

*At diagnosis 14 children had oral (*n* = 7)/oral+perianal (*n* = 4)/perianal (*n* = 3) disease only. At ≥2 years of follow-up, 5 children had oral (*n* = 1)/oral+perianal (*n* = 4) disease only. At ≥4 years of follow-up, 4 children had oral (*n* = 1)/oral+perianal (*n* = 3) disease.

9.6% (*P* = .02; OR, 0.43; 95% CI, 0.20–0.91) and a decrease in inflammatory disease (±perianal) from 91.2% to 82.7% (*P* = .005; OR, 2.16; 95% CI, 1.24–3.78). By 4 years after diagnosis, both stricturing disease (±perianal) and penetrating disease (±perianal) increased from 4.4% to 12.9% (*P* = .001; OR, 0.31; 95% CI, 0.14–0.67) and from 4.4% to 11.4% (*P* = .008; OR, 0.36; 95% CI, 0.16–0.79), respectively. Inflammatory disease (±perianal) decreased from 91.2% at diagnosis to 75.8% (*P* < .0001; OR, 3.32; 95% CI, 1.86–5.92). Perianal disease increasingly complicated the other behavior phenotypes over time, rising from 13.9% at diagnosis to 22.2% after 4 years of follow-up (*P* = .04; OR, 0.57; 95% CI, 0.34–0.98).

Phenotypic Characteristics of Childhood-Onset UC

UC phenotype was assessed at diagnosis and at last follow-up (Table 4). Pancolitis/extensive colitis was present in 74.7% at diagnosis. Of 95 children with childhood-onset UC, 73 had follow-up data recorded (median duration of follow-up, 3.5 years). At last follow-up, the proportions of disease location had not changed significantly. Of the 73 children with follow-up data available, 49 of childhood-onset UC already had the maximum extent (E3) at diagnosis. Of the 24 who could possibly increase extent at follow-up, forty-six percent extended their disease location from less extensive to extensive colitis/pancolitis (11/24).

Table 4. Comparison of Montreal Disease Location at Diagnosis and at Last Follow-Up in Childhood-Onset UC Patients

UC phenotype	At diagnosis (*n* = 95)	At last follow-up (*n* = 73)	*P*
E3	71 (74.7%)	60 (82.2%)	
E2	20 (21.1%)	12 (16.4%)	.39
E1	4 (4.2%)	1 (1.4%)	

Is There a Distinct Phenotype of Childhood IBD Diagnosed Before 8 Years of Age?

Of 408 participants, 82 (20.1%; 8/416 children had incomplete data) children were diagnosed with IBD before their 8th birthday (age cutoff as described by Heyman et al[7]; 53 CD [64.6%], 19 UC [23.2%], and 10 IBD type unclassified [IBDU; 12.2%]). Of the 326 children >8 at the time of diagnosis (79.9%), CD was diagnosed in 220 (67.5%), UC in 78 (23.9%), and IBDU in 28 (8.6%). At diagnosis in children <8, IBD was more likely to be localized to the colon (L2+UC+IBDU) than in older children (47/82 [57.3%] vs 145/326 [44.5%]; *P* = .03; OR, 1.68,95% CI, 1.03–2.73). CD presenting at <8 years was characterized by more isolated colonic disease (L2; 34.0% vs 17.7%; *P* = .009; OR, 2.39; 95% CI, 1.23–4.64), less ileal involvement (L1±L4 and L3±L4, 21/53 [39.6%] vs 133/220 [60.5%]; *P* = .006, OR, 0.43; 95% CI, 0.23–0.79) and less "panenteric" CD (L3+L4; 18.9% vs 33.6%; *P* = .03; OR, 0.46; 95% CI, 0.22–0.96). CD limited to the mouth and/or perianal region occurred more commonly in children <8 years at diagnosis (7/53 [13.2%] vs 6/220 [2.7%]; *P* = .001; OR, 5.43; 95% CI, 1.74–16.90).

Immunomodulator Use in Childhood-Onset IBD

The time to use of immunomodulatory drug therapy (first use of any of azathioprine, methotrexate, or biological therapy) was assessed and presented as Kaplan–Meier curves in the childhood-onset group only (Figure 1).

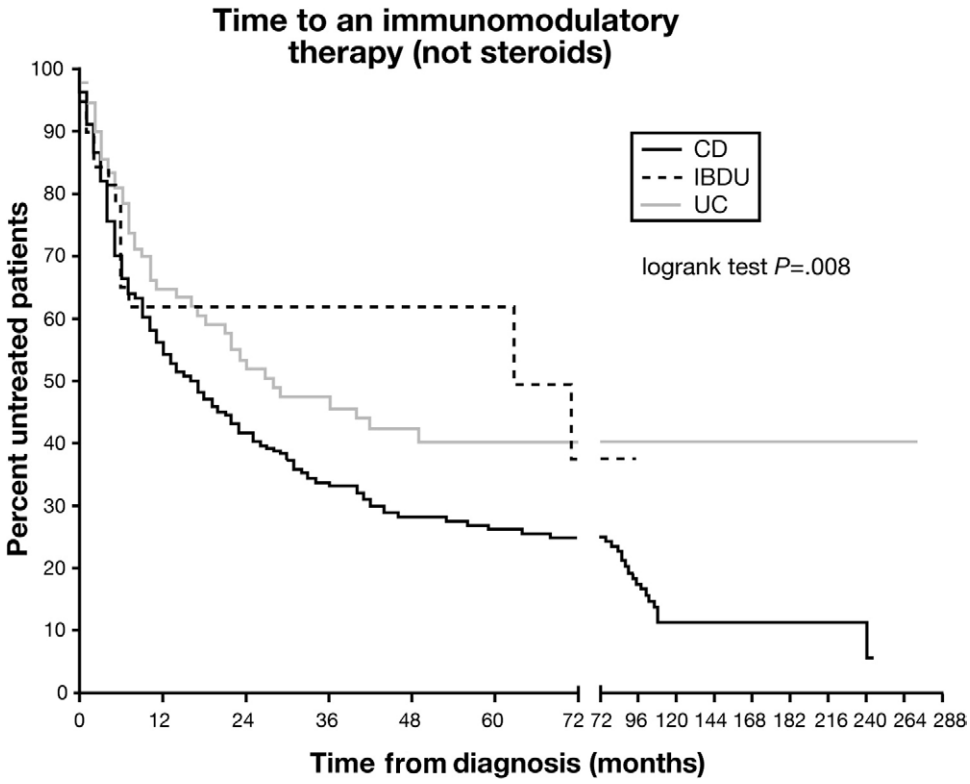

Figure 1. Kaplan–Meier curves showing time from diagnosis to first use of immunomodulatory drug therapy (any of azathioprine, 6-mercaptopurine, methotrexate, or biological therapy) in the cohort of childhood-onset IBD patients.

These data involve 408 cases, with missing data for the 8 (1.9%) remaining cases. There was a significant difference between these curves (log-rank test $P = .008$), with the median time to any immunomodulator usage 17 months for CD, 28 months for UC, and 63 months for IBDU. At 120 months of follow-up, the proportion of cases of CD, UC, and IBDU who had not been exposed to any immunomodulation were 11.5%, 40.5%, and 38.4%, respectively.

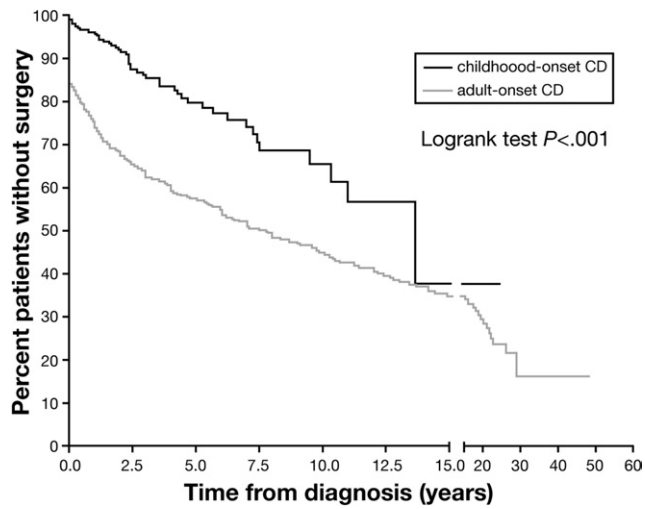

Figure 2. Kaplan–Meier curves showing time from diagnosis to surgery in childhood-onset and adult-onset CD.

Need for Resectional Surgery in Childhood-Onset and Adult-Onset IBD

Kaplan–Meier curves assessing the time from diagnosis to first resection/colectomy are shown for childhood-onset and adult-onset CD (data available for $n = 585$) and UC (data available for $n = 654$; Figures 2 and 3). Significant differences were seen in the Kaplan–Meier curves between the childhood-onset and adult-onset cohorts, in CD and UC (log-rank test $P < .001$ and $P = .03$, respectively).

Among the childhood-onset CD patients, 17.1% required surgery compared with 52.8% of adult-onset CD patients ($P < .0001$; OR, 0.18; 95% CI, 0.13–0.26). Five years after diagnosis, 20.2% of childhood-onset CD patients had undergone surgery versus 42.8% of adult onset CD patients. By 10 years of follow-up, these percentages were 34.5% and 55.5%, respectively. The median time to surgery in childhood-onset and adult-onset CD was 13.7 and 7.8 years, respectively (Figure 2).

Of childhood-onset UC patients, 20.0% underwent colectomy compared with 21.7% of adult-onset UC patients ($P = .70$; OR, 0.90; 95% CI, 0.53–1.54). At 5 years after diagnosis, 26.1% of childhood-onset UC patients had undergone surgery versus 15.5% of adult-onset UC patients. By 10 years of follow-up, 40.9% of childhood-onset UC patients and 19.9% of adult-onset UC patients had had a colectomy. Based on the Kaplan–Meier analysis, the median time to surgery was 11.1 years in childhood-onset UC compared with >50 years in adult-onset UC (Figure 3).

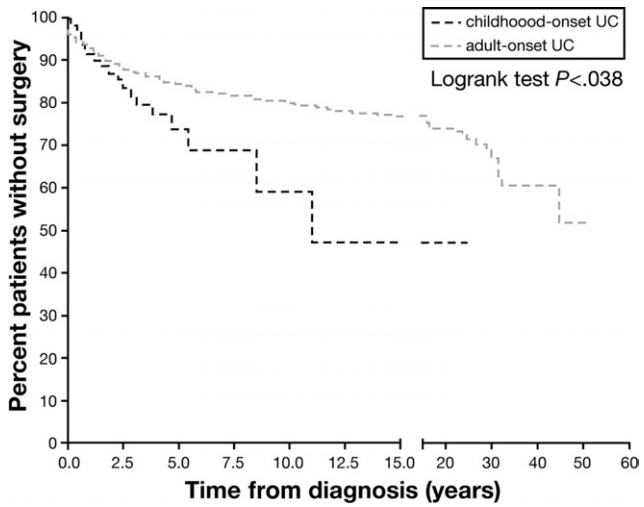

Figure 3. Kaplan–Meier curves showing time from diagnosis to surgery in childhood-onset and adult-onset UC.

Comparison of Childhood-Onset and Adult-Onset IBD: Location and Behavior Using the Montreal Classification

Phenotypic data on 416 children and 1297 adults with IBD were compared at the time of last follow-up (Table 5). In childhood-onset CD, there was a clear male predominance compared to adult-onset CD (59.4% vs 36.2%; $P < .0001$; OR, 2.58; 95% CI, 1.92–3.45). UC was equally likely to occur in both genders in childhood-onset and adult-onset disease. A family history of IBD (in any member of the family) was more common in childhood-onset than adult-onset disease (33.9% vs 19.6%; $P < .0001$; OR, 2.11; 95% CI, 1.65–2.69).

Location of CD (defined by the Montreal system as maximum extent by the time of last follow-up but before the first resection) showed statistically significant differences between childhood-onset and adult-onset disease ($P < .001$). Childhood-onset CD was characterized by less isolated ileal involvement (L1) 2.6% versus 31.5% ($P < .0001$; OR, 0.06; 95% CI, 0.03–0.12) and less isolated colonic disease (L2) 15.0% versus 36.1% ($P < .0001$; OR, 0.31; 95% CI, 0.21–0.46). Childhood-onset IBD was characterized by more "panenteric"/extensive CD (L3+L4; 43.2% vs 3.2%; $P < .0001$, OR, 23.36; 95% CI, 13.45–40.59).

To overcome the confounding factor of different investigation protocols in adult-onset and childhood-onset CD with regard to the use of upper GI endoscopy and small bowel assessment, we also analyzed the location of CD controlling for involvement of the GI tract proximal to the terminal ileum (L4) by means of a contingency table containing the categories L1±L4, L2±L4, L3±L4, and L4.

The extent of involvement of the GI tract in childhood-onset CD remained statistically different from adult-onset CD both when assessed at last follow-up and when only the patients with a minimum of 5 years follow-up were included (both $P < .001$; Supplementary Table 1 [available online at www.gastrojournal.org]). There is a highly significant association of ileal disease location with stricturing/penetrating disease behavior and of colonic disease location with inflammatory disease behavior when disease behavior is stratified for disease location in both childhood-onset and adult-onset CD after ≥5 years follow-up (Supplementary Table 1; $P < .001$). Comparing disease behavior at 5 years follow-up, the behavior of CD was similar in the 2 groups ($P = .17$).

UC in the childhood-onset cohort was more extensive ($P < .001$), with extensive colitis (E3) in 82.2% of childhood-onset but only 47.6% of adult-onset UC ($P < .0001$; OR, 5.08; 95% CI, 2.73–9.45).

Discussion

The present study represents not only a detailed application of the Montreal classification of IBD in a large cohort of patients with childhood-onset disease, but also provides new robust data on disease evolution, as well as need for immunomodulation and surgery in childhood-onset disease. Rigorous follow-up of 416 chil-

Table 5. Comparison of Location and Behavior Between Childhood-Onset and Adult-Onset IBD Patients Using the Montreal Classification

	Scottish childhood-onset IBD	Scottish adult-onset IBD
n	416	1297
	At last follow-up (*n* = 273)	At last follow-up (*n* = 507)
CD phenotype: Location*		
L1	7 (2.6%)	160 (31.5%)
L2	41 (15.0%)	183 (36.1%)
L3	52 (19.0%)	99 (19.5%)
L1 + L4	5 (1.8%)	21 (4.1%)
L2 + L4	43 (15.8%)	8 (1.6%)
L3 + L4	118 (43.2%)	16 (3.2%)
L4	2 (0.7%)	13 (2.6%)
P	<.001	
	At 5 years (*n* = 136)	At 5 years (*n* = 377)
CD phenotype: Behavior		
B1 (±p)	99 (72.7%)	249 (66.0%)
B2 (±p)	20 (14.7%)	54 (14.3%)
B3 (±p)	17 (12.6%)	74 (19.7%)
P	.17	
	At last follow-up (*n* = 73)	At last follow-up (*n* = 569)
UC phenotype		
E3	60 (82.2%)	271 (47.6%)
E2	12 (16.4%)	201 (35.3%)
E1	1 (1.4%)	97 (17.0%)
P	<.001	

*Five children had oral (*n* = 1)/oral+perianal disease (*n* = 4); 7 adults had oral (*n* = 4)/oral+perianal (*n* = 1)/perianal (*n* = 2) disease.

dren with IBD in the 3 pediatric gastroenterology centers in Scotland has allowed us to document these aspects, notably the progression of disease location and behavior. Data were collected by structured case notes review, and measures taken to overcome interobserver bias.

A number of our findings are likely to be important and pertinent both to basic research and to clinical practice, and may be useful in patient counseling. We have demonstrated that the presenting phenotype of childhood-onset IBD was characterized by extensive anatomic involvement, with strikingly high rates of panenteric CD (small bowel, large bowel, and upper GI tract involvement) as well as extensive UC. Furthermore, disease extent was remarkably dynamic in childhood-onset disease: Even within 2 years of diagnosis, childhood-onset CD progressed to more extensive anatomic involvement in >1 in 3 patients. Disease behavior rapidly progressed to complications of stricture formation or the development of fistulae. Disease extent in 46% of the few cases of childhood-onset UC with isolated left-sided disease or proctitis at diagnosis also showed extension within the follow-up period.

We have provided compelling evidence for the high prevalence of an extensive or panenteric disease phenotype at presentation in childhood-onset CD. Recent data from the North American Pediatric IBD Consortium Registry are consistent with our findings, albeit using a distinct disease classification system.[9] Gupta et al presented their findings in 600 pediatric CD patients at diagnosis: 61.5% of children had small bowel and colon involvement (compared with 50.5% in our study). Baldassano et al[17] recently described a small cohort of 142 children with CD: 86% had involvement of the small bowel and colon (± upper GI tract). Cucchiara et al[18] showed in an Italian cohort of pediatric CD patients with ≥1 year of follow-up (n = 200) that 58% had ileocolonic CD (using the Vienna classification).[18]

Our data in UC are also consistent with the hypothesis that childhood-onset disease has a very high bias toward extensive disease. This observation is also consistent with other datasets. Previously reported rates of pancolitis in patients with UC, from prospective childhood studies (80%–90%)[7,19,20] are far higher than those from prospective adult studies (24% pancolitis[21] or 33% extensive colitis[22]). Our study not only provides further replication of these data, but also directly compares a childhood-onset and adult-onset cohort within the same population using the Montreal classification (82% of childhood-onset UC patients had extensive colitis at last follow-up compared with 47% of adult-onset UC).

Moreover, we provide evidence that disease phenotypic characteristics are dynamic, and changeable, rather than stable, in childhood-onset disease. Detailed analysis of our patients with childhood-onset CD demonstrated that the anatomic extent of disease progressed to more extensive involvement soon after diagnosis in 39%. In the vast majority, these changes were not due to the inclusion of findings on upper GI endoscopy but rather to progression from limited disease (oral/perianal [L1, L2, or L4]) to involve both small and large bowel (L3). In almost 50% of patients who progressed in anatomic involvement, this was due to involvement of the ileum. These data contrast with the stability of disease location repeatedly reported in adult CD.[23,24] Louis et al[23] followed 125 adult patients with CD and found, at 10 years after diagnosis, that only 15% had changed disease location (location was defined using the Vienna classification). Henriksen et al[24] observed a change of (Vienna) CD location in 13.5% after 5 years follow-up (n = 200).

In our CD cohort, our data intriguingly suggest heterogeneity even within childhood-onset phenotype. We have shown that involvement of the ileum is age dependent: children <8 years old at the time of diagnosis had significantly less involvement of the ileum and more isolated colonic disease than children >8 years at diagnosis, confirming previous studies.[7,8,25] In a large study of nearly 1400 North American early-onset patients, Heyman et al[7] demonstrated by multifactorial analysis that a colonic predominant phenotype exists in IBD diagnosed under the age of 8 years. Paul et al[8] studied 413 pediatric IBD patients and also demonstrated a greater tendency for very young patients to present with colonic disease.

In addition to the dynamic nature of disease location, we have also demonstrated that childhood-onset CD behavior was not stable over time: Inflammatory disease behavior progressed with the development of stricturing/intestinal penetrating complications. This progression is also seen in adult-onset disease (Table 5). In the landmark study of disease behavior in 2000 CD patients, Cosnes et al[26] demonstrated that 40% had penetrating disease as defined by the Vienna criteria at 5 years and 70% by 20 years. Similar data from Belgium and Scotland were reported subsequently.[27,28] Detailed analysis of disease behavior stratified for disease location demonstrated a highly significant association of stricturing/penetrating disease complications with ileal CD and of inflammatory disease with colonic CD (both in childhood-onset and adult-onset CD; Supplementary Data [available online at www.gastrojournal.org]).

Direct comparison of the phenotypic characteristics in adult-onset and childhood-onset disease also emphasized the extensive intestinal involvement in children, although these comparisons are limited by the retrospective nature of the present study. The increased intensity of investigation in childhood-onset disease compared with adult-onset IBD is noteworthy.[13,14,29] This line of argument has been previously suggested to underlie the high prevalence of upper GI disease reported in children, when compared with adults—upper GI endoscopy is rarely performed in adult IBD assessments and historic (adult) datasets typically have less small bowel assessment. Notwithstanding this issue, which is difficult to resolve without a longitu-

dinal prospective study both in children and adults, analysis based on the Montreal categories, which treats upper GI disease as a modifier (ileal, colonic, or ileocolonic disease each with or without CD proximal to the terminal ileum), confirmed the statistically significant differences between CD location in childhood-onset and adult-onset onset CD.

In an attempt to further define the "severity" of childhood-onset IBD, we evaluated the need for both immunomodulation and surgery (Figures 1–3). By 12 months from diagnosis, 45.9% of childhood-onset CD, 37.9% of IBDU and 35.1% of UC have commenced immunomodulator therapy. However, interpretation of these data as a surrogate for severity is problematic, and confounded by multiple factors, most notably the variability amongst individual physicians in thresholds for the use of these agents. Physician preferences have undoubtedly changed in the last decade, both for adults and in children. Increasing use of immunomodulatory therapy early in the course of disease has become a well-established treatment paradigm in pediatric IBD practice, following the landmark publication by Markowitz et al[30]; in adults, data from our own center clearly illustrate similar temporal trends toward early use—significantly higher rates of 6-mercaptopurine/azathioprine usage of 47.9% at 12 months were seen in an inception cohort diagnosed between 2003 and 2007 compared with a rate of 13.3% in a cohort diagnosed between 1998 and 2002.[31]

Many may regard the need for surgery after diagnosis as a potential "gold-standard" marker of disease severity. For this reason, we have analyzed need for surgical intervention in our cohort. Intriguingly, these data suggest that surgical intervention may occur earlier in childhood-onset UC than in adult-onset UC, but that the opposite relationship is seen for CD. However, there are multiple possible confounding variables in using these data as a surrogate for severity, especially when comparing practice for children and teenagers with CD against practice in adults. The more extensive panenteric disease of childhood-onset CD may preclude referral for early surgery, as do the frequently strong reservations of children and their families concerning early surgical intervention (especially if formation of a stoma is required). We suggest that these factors impact significantly on the data in childhood-onset CD, and lead to the escalation of medical therapy rather than surgery, notwithstanding disease severity. In UC, the higher surgical rates we demonstrate in childhood-onset disease are interesting, in the context of the high prevalence of extensive colonic involvement in these children, and may well reflect "severity" more accurately. Notwithstanding these controversies, the different trends in time to first surgery in childhood-onset CD and UC are of interest and require further evaluation.

The findings of our study may have clinical implications for management in childhood-onset IBD. It might be considered that early use of biological agents and immunosuppressants may ideally be targeted preferentially on children with aggressive disease. However, it is increasingly apparent that other factors need also be considered in highlighting either all or a subgroup of childhood-onset IBD as the group for whom "top-down" intervention is appropriate—most notably the recent concerns regarding the development of hepatosplenic T-cell lymphoma in patients treated with combined immunomodulation, together with the lack of any evidence-based strategies for discontinuation of anti-tumor necrosis factor therapies, or even thiopurines.[32]

Thus, we propose that the initial application of our data may be in the translational research setting. Identifying specific laboratory markers of disease susceptibility or phenotype—genetic, serologic, or proteomic—critically depends on the availability of an appropriate classification system. Our study has applied the Montreal classification in a large cohort of childhood-onset IBD patients, and demonstrates the potential usefulness of this system in studies of pediatric IBD.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.06.081.

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