Definition of Phenotypic Characteristics of Childhood-Onset Inflammatory Bowel Disease

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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-