Natural History of Crohn's Disease: Comparison Between Childhood- and Adult-Onset Disease

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Background: Childhood-onset Crohn's disease (CD) might reflect a more severe form of disease. To test this hypothesis we analyzed the long-term natural history of CD in an adult cohort of patients with childhood-onset compared to adult-onset CD.

Methods: We selected 206 childhood-onset CD patients among 2992 adult patients with a diagnosis of CD established before December 31, 2000. Disease characteristics were prospectively assessed during follow-up until December 2007 and compared to adult-onset CD patients matched 2 to 1 on gender, year of CD diagnosis, and disease location.

Results: Compared to adult-onset CD, patients with childhood-onset CD were more likely to have a severe disease, with an increased year-by-year disease activity index (37% of patient-years in childhood-onset group versus 31% in the adult-onset group, $P < 0.001$). Immunosuppressant requirement was also increased with a 10-year cumulative risk of 54 ± 3% in childhood-onset CD group versus 45 ± 2%, in the adult-onset CD group ($P < 0.001$). Cumulative risks of stricturing and penetrating complications and surgical resections were not statistically different between groups. Accordingly, these events occurred at a younger age in the childhood-onset CD group. At the age of 30 years the actuarial risk of having undergone an extensive intestinal resection was 48 ± 5% in the childhood-onset group versus 14 ± 2% in the adult-onset group ($P < 0.001$).

Conclusions: Patients with childhood-onset CD exhibit a more active disease and require more immunosuppressive therapy. This feature is observed irrespective of the disease location, suggesting an intrinsic more severe phenotype.

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Crohn's disease (CD) generally affects young adults in the third decade of life. However, ≈10% of patients develop their disease before the age of 17 years.[1,2] Recent epidemiological studies also suggest an increase in the incidence of childhood-onset inflammatory bowel diseases (IBD), particularly for CD over the past 10 years.[3–5] These studies showed incidence rates of CD ranging between 2–5 per 100,000 children per year.[2] The recent Montreal Classification of CD makes it possible to separate childhood-onset disease from adult forms as a new category.[6] This change contributes largely to a systematic review and analysis of early-onset pediatric from adult forms of CD. Indeed, there are clear differences: when compared to adult CD, childhood-onset CD is characterized by a higher proportion of males,[7] an increased prevalence of jejuno-ileitis,[8,9] and a more frequent requirement of second-line immunosuppressants.[10,11] There are preliminary data suggesting that disease behavior might be more severe compared to adult CD.[12,13] However, limited information is available on long-term clinical outcomes of childhood-onset CD. The natural course and evolution of CD depends on the initial location of CD lesions, a major determinant for the development of stricturing and penetrating intestinal complications.[14,15] To assess the particular severity of childhood-onset CD, there is a need for comparing such patients with adult-onset CD and similar disease location.

The main objective of the present study was to describe the long-term natural history of CD in a large cohort of patients with childhood-onset of disease compared to patients with adult-onset CD exhibiting the same initial presentation with regard to disease location. To compare and detect potential differences between pediatric and adult onset CD, the matched groups were analyzed at identical timepoints of disease duration.

MATERIALS AND METHODS

Childhood-onset CD Patients

The patients were selected from the MICISTA Registry, a tertiary clinical database of more than 6000 IBD

patients evaluated by the same staff of physicians at Rothschild Hospital (1974–2002), then St-Antoine Hospital (from 2003 up to now) in Paris. The registry was built during the year 1994. Data were collected retrospectively before 1994 and prospectively for patients entering the database after 1994. In December 2007 there were 2992 patients with a diagnosis of CD established before December 31, 2000. This date was chosen to analyze each patient in a suitable follow-up period to assess the long-term natural history of the disease. Among this population we selected 206 consecutive patients with an initial diagnosis of CD before the age of 16 years (childhood-onset CD). Among them, 4 patients had an initial diagnosis of ulcerative colitis or undetermined colitis, with this diagnosis changed to CD before their 16th birthday. Patients who changed their diagnosis subsequently were not included. Patients with oral or perianal lesion without intestinal involvement were also excluded ($n = 3$). Diagnosis of CD in children was based on the Porto criteria.[2] Adult CD patients satisfied the Lennard–Jones criteria.[16] Patients transferred from pediatric centers to our adult care center were treated during childhood in pediatric centers located in Paris (Hôpital Trousseau, Hôpital Robert-Debré, and Hôpital Necker-Enfants Malades), except for 12 adolescent patients managed since diagnosis in our adult care department. As our center and Hôpital Trousseau are closely located, we were able to take care of 100% of the patients coming from this hospital. Considering the 2 other hospitals, proportions of transfer varied depending on patient geographical housing. Median age at transfer was 17 years (range: 15–21). Considering total follow-up of the childhood-onset CD cohort, pediatric management represented 18% of the total time (385 patient-years in 82 patients). For this subgroup and during this period, data regarding treatments and activity were assessed retrospectively.

Adult-onset CD Control Group

Control patients were selected from the 2786 CD patients diagnosed after 16 years of age before December 2000. We matched 2 adult-onset CD patients to 1 childhood-onset CD patient. The matching procedure was anonymous and made on gender, calendar year of CD diagnosis (boxes of 5 years), and disease location according to the Montreal Classification.[6]

Characteristics of CD

The time at diagnosis was defined as the date of first detection of unequivocal inflammatory abnormalities of the intestine, as assessed from radiological, endoscopic, or perioperative observations. Initial location of CD lesions was determined by colonoscopy and small bowel follow-through or computed tomography (CT) scan. After diagnosis, patients were clinically followed up via 3 to 4 visits per year. After diagnosis, investigations were mandatory in case of flare-up or development of new symptoms. Morphological investigations included proctosigmoidoscopy, colonoscopy, CT scan, and small bowel x-ray. Upper gastrointestinal endoscopy was performed only in case of gastroesophageal symptoms. Patients were routinely examined for perianal disease at each visit.

Location and anatomic complications of CD were classified according to the Montreal Classification.[6] First morphological demonstration of narrowing (stenosing) or penetrating complication was used to date the occurrence of this complication.

Weight and height were noted at the last visit for all patients and the body mass index (BMI) was then calculated. Of note, most of the patients from the childhood-onset CD group were adults at the last visit, giving a valid picture of the final height.

Treatment of CD

Most childhood-onset CD patients were managed successively by 2 groups of physicians. In the great majority of cases, the step-up strategy of management was followed. In children, enteral nutrition was most often used as first-line therapy, before steroids, in association with 5-aminosalicylates. In adults, flare-up episodes were treated with mesalamine (3–4 g daily) or prednisolone (1 mg/kg per day, progressively tapered after 4 weeks), according to clinical severity. When steroid therapy failed or was contraindicated, both children and adults seen before 1999 were given a 3–8-week course of enteral or parenteral nutrition; those seen after June 1999, when infliximab became available in France, received infliximab (5 mg/kg). Adalimumab was used as second-line anti-tumor necrosis factor (TNF) drug after 2006.

As maintenance treatment, aminosalicylates (2–3 g daily) were used for asymptomatic or moderately active forms of the disease. Immunosuppressants were proposed in case of severe CD (steroid-dependent or poorly responsive to steroids). Azathioprine (2 mg/kg per day) was used as a first-line immunosuppressive drug. In case of repeated flare-ups or chronic active disease in a patient receiving azathioprine, the drug dosage was increased to 2.5–3 mg/kg per day. Intramuscularly or subcutaneously administered methotrexate (20–25 mg weekly) was used in patients unresponsive or intolerant to azathioprine.

Although the overall strategy remained mostly unchanged, there was in our 3 pediatric and adult centers a clear tendency over time to initiate immunosuppressants earlier in the disease course.[17] Surgery was limited to stenotic and extraparietal complications or intractable forms after a well-conducted medical management.

Severity of CD

Severity of the disease was prospectively analyzed from January 1995 to last visit until December 2007. Activity of the disease was assessed by a year-by-year activity index taking into account the occurrence of a flare-up each year. For this type of analysis we considered that CD scores such as the Crohn's Disease Activity Index was not sufficient to define a flare. Thus, a flare-up was defined as a modification of the symptoms leading to a change in CD treatment. Each patient-year was considered as active disease if a flare-up or a complication occurred during the year, and as inactive disease in the other cases. Activity in the childhood onset and the adult-onset CD group was compared year-by-year using the percentage of active patients in each group. This way of analyzing activity of the disease was used as previously described by Munkholm et al.[18]

Treatment Requirement

In parallel to the severity of disease phenotype, we also took into account treatment requirement. Thus, the need and intensity of the treatments were analyzed retrospectively (for the period before 1995) and prospectively (after January 1995) from our database, except in the subset of patients who were still receiving pediatric care after January 1995 who were retrospectively included. We collected data regarding medical therapy, i.e., need for glucocorticosteroids, nutritional support, immunosuppressant (purine analogs, methotrexate, anti-TNF antibodies) and finally incidence and extent of excisional surgery (intestinal resection of any type, establishment of a permanent stoma, and large intestinal resection, either alone or cumulative, defined by a postsurgical index). We did not study stricturoplasty. The postsurgical handicap index (PSHI) was developed to predict the functional consequences of intestinal resection for CD.[19] This index is calculated from operative records, taking into account the location and the extent of intestinal resection. An index score equal or superior to 20 has a high predictive value of diarrhea following intestinal resection. Patients with a transient stoma, but in whom intestinal continuity has not been restored at the last visit for more than 5 years, were considered as having a permanent stoma. We assessed both the cumulative number of patients requiring these medical therapies or type of surgery and the time to initiation of therapy or surgical event.

Statistical Analysis

Continuous data are expressed as mean (standard deviation, SD), and differences between the groups were tested for significance by Student's paired *t*-test. Discrete data are given as percentages and comparisons were made with a Pearson chi-square test. For actuarial analysis, the Kaplan–Meier model was used, with date of birth or date of diagnosis as starting points. The curves were compared by the log-rank test. Calculations were performed using GB-stat statistical software (Silver Spring, MD).

RESULTS

Comparability of the 2 Groups

Two hundred and six patients were included in the pediatric group: 114 males (55%) and 92 females (45%), and 412 patients in the adult group (Table 1). Follow-up was complete in 475 patients (including 18 deceased). Contact by mail or phone was attempted in the remaining 146 patients but only 30% could be contacted. Finally, updated data were available in 519 patients (84%), with a similar proportion between the pediatric and the adult group (166 patients [81%] and 353 patients [86%], respectively).

The groups were matched according to calendar year and disease location at diagnosis. The proportion of patients referred from hospitals out of the Paris area was identical. The majority of patients were of Caucasian origin. Other significant differences between the 2 groups were appendectomy rate and smoking habits (Table 1). Median age at diagnosis was 13 years (range: 4–15) in the childhood-onset group. Twelve percent were diagnosed before 10 years old, 22% between 10 and 11 years, 32.5% between 12 and 13 years, and 33.5% after 14 years old. For the adult-onset group, median age at diagnosis was 28 years (range: 16–54) with 12% (48 patients) above 40 years old. Median age at last visit was 26 years (range: 18–59 years) in the childhood-onset CD group, and 45 years (22–79 years) in the adult-onset CD group. Eighteen patients died, 2 in the childhood-onset CD group (1 had short bowel syndrome, the other developed postoperative septic complications) and 16 adults (the death was directly or indirectly related to CD in 9 cases). The median disease duration was 14.7 years (range: 10.8–45.2 years) in the pediatric group and 15.8 years (range: 10.4–47.9 years) in adults.

Height and Weight

The mean final adult height was significantly lower than that of adult-onset CD patients (Table 2). This difference was significant in men, with 3 cm less in patients diagnosed with CD during childhood compared to men diagnosed in adulthood, whereas the difference was not significant in women. Sixteen childhood-onset CD patients (10 males, 6 females) had a height less than the French mean −2 SD (164 cm for males, 153 cm for females) versus 14 in the adult-onset group (6 males, 8 females) ($P = 0.02$). Considering the same patients, weight and BMI of childhood-onset patients were significantly lower than those in the adult-onset group for both genders. There were 20

TABLE 1. Mean Characteristics of the Childhood-onset CD and Adult-onset CD Patients

	Childhood-onset CD (n=206)	Adult-onset CD (n=412)	P
Median age at diagnosis, years (range)	13 (4–15)	28 (16–54)	—
Male (%)	114 (55)	228 (55)	NA
Calendar year of diagnosis			
Before 1980 (%)	35 (17)	71 (17)	NA[a]
1981–1990 (%)	68 (33)	137 (33)	NA
1991–1995 (%)	56 (27)	111 (27)	NA
1996–2000 (%)	47 (23)	93 (23)	NA
Initial disease location			
Ileal, L1 (%)	76 (37)	156 (38)	NA
Colonic, L2 (%)	54 (26)	106 (26)	NA
Ileocolonic, L3 (%)	74 (36)	145 (35)	NA
Isolated proximal disease, L4 (%)	2 (1)	5 (1)	NA
Associated proximal lesions (%)	31 (15)	60 (15)	NA
Perianal lesions (%)	62 (30)	105 (25)	NS
Extraintestinal manifestations (%)	78 (38)	152 (37)	NS
Living less than 100 km away from Paris	144 (70)	292 (71)	NS
Family history of IBD (%)	48 (24)[b]	70 (17)	0.05
Prior appendectomy (%)	12 (6)	118 (29)	<0.001
Smoking status			
Never (%)	139 (68)	148 (36)	<0.001
Current at diagnosis (%)	20 (10)	257 (63)	
Start after diagnosis (%)	45 (22)	2 (0.5%)	
Unknown	2	5	
Median disease duration, years (range)	14.6 (9.5–45.2)	15.8 (0.6–47.9)	NS

[a]NA, not applicable, the matching was based on these criteria.
[b]Three children were adopted.

childhood-onset CD patients who had a BMI under 17 versus 16 in the adult-onset group ($P < 0.01$).

Year-by-Year Disease Activity Between 1995–2007

Activity of the disease tended to decrease with time in both groups (Fig. 1). However, there were constantly higher proportions of patients with active disease every year among the childhood-onset CD group versus the adult-onset CD group. In total, during the years 1995–2007 (6585 patient-years), CD was active in 37% of patient-years in childhood onset CD, versus 31% in adult onset CD ($P < 0.001$). This difference remained significant when analyzed separately for patients diagnosed before and after 1990 (data not shown).

In parallel, looking only at the immunosuppressant requirement during the same period (1995–2007), a higher proportion of treated patients was observed in the childhood-onset CD group (41% of patients-years) compared to

TABLE 2. Anthropometric Characteristics at the Last Visit (mean ± SD) in Childhood-onset and Adult-onset CD

	Childhood-onset CD (n=206)	Adult-onset CD (n=412)	P
Height (cm)			
Males	172.8 ± 7.4	176.4 ± 6.5	<0.001
Females	162.2 ± 5.9	163.1 ± 6.0	NS
Total	167.9 ± 8.6	170.3 ± 9.1	<0.001
Weight (kg)			
Males	60.8 ± 10.1	72.9 ± 14.0	<0.001
Females	52.2 ± 7.7	59.7 ± 13.4	<0.001
Total	56.8 ± 10.1	66.8 ± 15.2	<0.001
Body mass index			
Males	20.3 ± 2.8	23.4 ± 4.3	<0.001
Females	19.8 ± 2.5	22.4 ± 4.5	<0.001
Total	20.1 ± 2.7	22.9 ± 4.5	<0.001

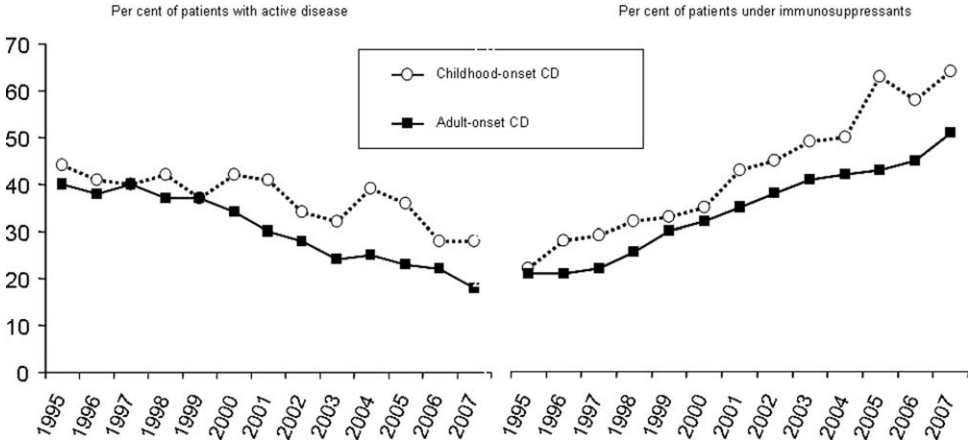

FIGURE 1. Year-by-year disease activity and immunosuppressant therapy during the 1995–2007 period (prospective follow-up) in patients with childhood-onset CD versus adult-onset CD. Left side: Each year percents of patients with active disease in childhood-onset CD versus adult-onset CD, $P < 0.001$. Right side: Each year percents of patients using immunosuppressants in childhood-onset CD versus adult-onset CD, $P < 0.001$.

the adult-onset CD group (33% of patient-years, $P < 0.001$) (Fig. 1, right). Moreover, from 1999 to 2007 anti-TNF-therapy was used in 10.5% of patient-years in the childhood-onset group versus 3.5% of patient-years in the adult group ($P < 0.001$).

Treatments

Treatments received at any time during the course of the disease are indicated in Table 3. Although enteral nutrition was used largely in childhood-onset CD, the number of patients who eventually required steroids was higher than in the adult-onset group. Immunosuppressants (including anti-TNF) were also significantly more often required in childhood-onset CD. This increased requirement of immunosuppressants was confirmed by the actuarial analysis. The 5-year and 10-year cumulative risk of requiring immunosuppressive therapy were 31 ± 3% and 54 ± 3%, respectively, in the childhood-onset group versus 27 ± 2% and 45 ± 2% in the adult-onset group, respectively ($P < 0.001$). Table 4 shows the percentage of patients naïve to immunosuppressants in whom this treatment was initiated according to 3 calendar periods in the 2 cohorts. The difference was significant only after 2000.

In contrast, there was no significant difference between the 2 groups for the need of surgery. More than half of the patients needed excisional surgery in both groups, and the total number of intestinal resections was 206 in 124 patients with childhood-onset CD (1 every 16.6

TABLE 3. Cumulative Therapeutic Requirements (Number and % of Patients) in Childhood-onset and Adult-onset CD Groups

	Childhood-onset CD (n=206)	Adult-onset CD (n=412)	P
Medical requirements			
5-aminosalicylates (%)	205 (100)	410 (100)	NS
Steroids (%)	198 (96)	376 (91)	0.03
Azathioprine or 6-mercaptopurine (%)	148 (72)	251 (61)	<0.01
Methotrexate (%)	39 (19)	41 (10)	<0.01
Anti-TNF (%)	53 (26)	55 (13)	<0.001
Enteral nutrition (%)	75 (36)	45 (11)	<0.001
Parenteral nutrition (%)	42 (20)	43 (10)	<0.001
Surgical requirements			
Intestinal resection (%)	124 (60)	250 (61)	NS
More than 1 intestinal resection (%)	50 (24)	97 (24)	NS
Permanent stoma (%)	24 (12)	30 (7)	0.07
Perianal surgery (%)	88 (43)	156 (38)	NS

TABLE 4. Patients (Percentage and Numbers) Naïve to Immunosuppressive Therapy in Whom Immunomodulators (IMs) Were Started Within 3 Consecutive Calendar Periods in Childhood-onset and Adult-onset CD Groups

	Childhood-onset CD Group	Adult-onset CD Group	*P*
<1995	31% (46/148)	25% (76/301)	0.19
1995–2000	37% (59/160)	33% (111/336)	0.40
2001–2007	43% (43/101)	28% (64/225)	0.01

In parentheses, number of patients in whom IMs were started during the considered period/number of the total cohort during the considered period.

years), versus 392 in 250 patients with adult-onset (1 every 17.9 years). The cumulative risk of surgery from the date of diagnosis of CD was not significantly different between the 2 groups (Fig. 2). The cumulative extent of resection tended to be higher in childhood-onset CD (median postsurgical handicap index 26 [interquartile range 18–42]) compared to adult-onset CD (median value 22 [interquartile range 17–31]) ($P = 0.06$). The risk of having an extensive (PSHI >20) intestinal resection was similar (Fig. 2). Three childhood-onset CD patients and 2 adult-onset CD patients developed short bowel syndrome requiring prolonged parenteral nutrition. The 25-year cumulative risk of permanent stoma was 17 ± 4% in the childhood-onset group versus 10 ± 2% in the adult-onset group ($P = 0.05$).

As expected, significant differences appeared between the groups when postsurgical sequelae were related to age (Fig. 2). At the age of 30 years, the risk of having undergone an extensive intestinal resection, i.e., at high risk of functional sequelae, was 48 ± 5% in the childhood-onset group versus 14 ± 2% in the adult-onset group ($P < 0.001$), and the risk of permanent stoma was 12 ± 3% in childhood-onset patients versus 1 ± 0.5% in adult-onset patients ($P < 0.001$).

Complications

Figure 3 gives the cumulative survival curves of the lack intervals from diagnosis to the first complication in form of intestinal stricture, intestinal perforation, and perianal fistula, respectively, in the 2 groups. Overall, the cumulative risks of these complications were similar in the 2 groups. As an example, at 10 years, comparing adult-onset and childhood-onset CD groups, proportions of patients free of stricture were 75.3% (SD 2.2) versus 78.2% (SD 2.9) ($P = 0.16$), respectively; proportions of patients free of perforation were 73.0 (SD 2.3) versus 74.1% (SD 3.2) ($P = 0.14$); and finally, proportions of patients free of perianal disease were 75.3% (SD 2.2) and 78.2% (SD 2.9) ($P = 0.35$).

Eleven cases of bowel adenocarcinoma occurred during the CD course. Five of them were observed in the childhood-onset CD group (3 colonic and 2 small bowel adenocarcinoma) and 6 in the adult-onset CD group (2 colonic and 4 small bowel adenocarcinoma). The delay between diagnosis of the disease and adenocarcinoma was 25.1 ± 8.7 years in the childhood-onset CD group versus 15.2 ± 10.0 years in the adult-onset CD group ($P < 0.05$). Median age at diagnosis of adenocarcinoma was 42.6 ± 3.9 years in the adult-onset group and 36.2 ± 10.9 years in the pediatric one (NS).

DISCUSSION

This study was designed to compare the clinical course of matched cohorts with early-onset (childhood-onset) or late-onset (adult-onset) forms of CD. As indicated, we revealed several distinctive features of childhood-onset CD. In comparison with an adult cohort of CD patients with similar location, the patients with childhood-onset CD were more likely to have severe disease. Indeed, in childhood-onset CD patients an increased frequency of periods with active disease was observed, whereas immunosuppressant requirement was also increased. However, the occurrence of stricturing and penetrating complications and the surgery rate were not different between the 2 groups, although the surgical sequelae tended to be more important and occurred at a markedly younger age in patients with childhood-onset CD.

A potential source of selection bias could have been that some patients with childhood-onset CD may not reflect the general childhood-onset CD population, as a rather benign disease course might not require specialized consultation during adulthood. However, in our practice over 95% of pediatric IBD patients were transferred at the age of 18 years to a tertiary care adult GI center. More precisely, 100% of the patients from 1 of the 3 pediatric GI units (Trousseau Hospital) of the childhood-onset cohort have been seen at least once in our unit after 7 years of follow-up. In addition, the great majority of children with IBD in France are managed in academic centers, whereas in adults only the most difficult cases are seen at referral centers. Thus, potential recruitment bias may have led to an overrepresentation of severe cases among the adults. In this setting, analysis of the complication rates may have been jeopardized by the difference in recruitment. Despite this bias, more active disease was seen in childhood-onset CD patients.

Few reports have focused on the natural history of childhood-onset CD. To our knowledge, only 1 study compared the outcome of pediatric patients compared to patients diagnosed after age 18 years.[13] Freeman[13] showed

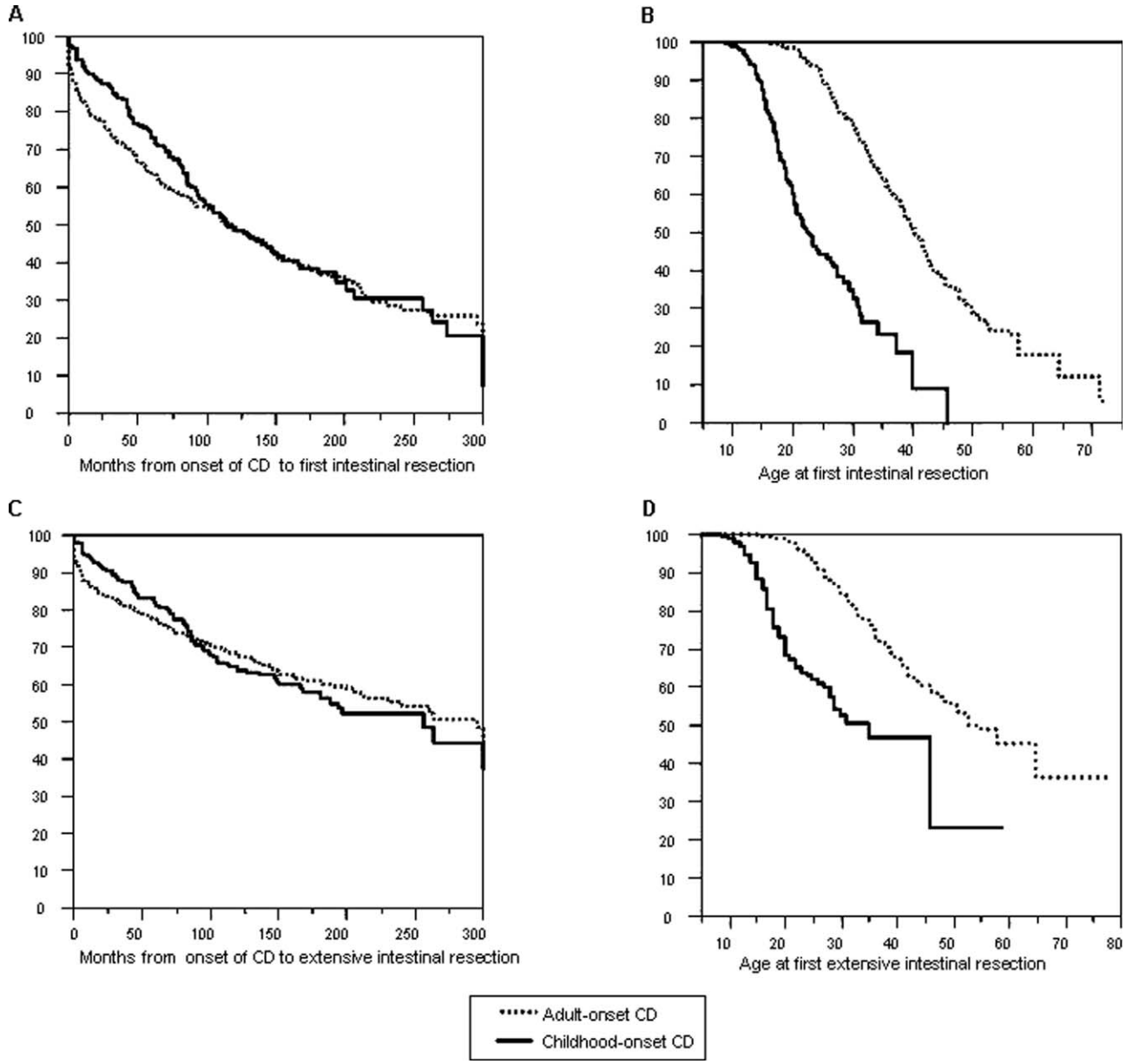

FIGURE 2. Kaplan--Meier curves of intestinal resection-free survival in patients with childhood-onset CD versus adult-onset CD. (A) Estimated risk of intestinal resection from CD diagnosis. (B) Estimated risk of intestinal resection from birth. $P < 0.01$. (C) Estimated risk of extensive intestinal resection from CD diagnosis. (D) Estimated risk of extensive intestinal resection from birth. $P < 0.01$.

that there was no difference in the occurrence of long-term complications between CD patients with adult versus pediatric onset of disease. We did not find any difference in the occurrence of intestinal stricture, intestinal perforation, or perianal fistula. Similarly, the need for surgery and mean PSHI (extent and location of the resection) were not significantly different. This latest result suggests that the surgical approach was not much different in the 2 groups. The surgical recurrence risk was not increased compared to adult-onset CD, contrasting with other studies.[20] However, post-surgical sequelae occurred earlier in life.

An important finding of our study was the increased disease activity in childhood-onset CD patients compared to adult-onset CD. This difference was documented in patients with an identical duration of disease despite a more significant medical regimen (more immunosuppressants, more biologics). Moreover, current smoking, which is recognized as an important deleterious factor in CD,[21]

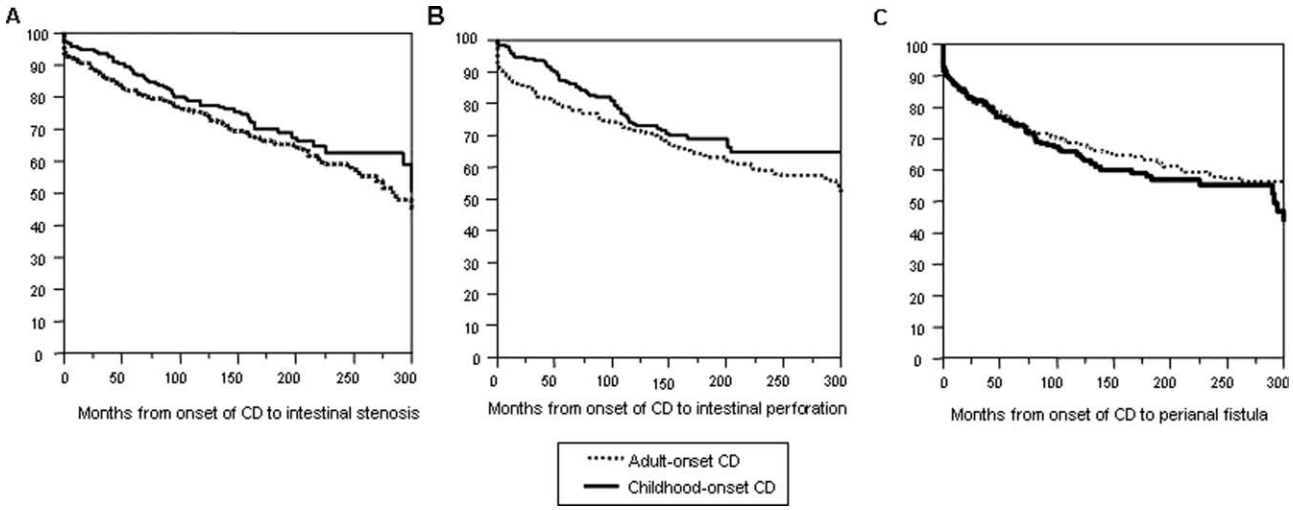

FIGURE 3. Kaplan--Meier curves of complication-free survival in patients with childhood-onset CD versus adult-onset CD. (A) Kaplan--Meier estimates of the time to intestinal stricture among patients with childhood-onset and those with adult-onset CD. (B) Kaplan--Meier estimates of the time to intestinal perforation among patients with childhood-onset and those with adult-onset CD. (C) Kaplan--Meier estimates of the time to perianal fistula among patients with childhood-onset and those with adult-onset CD.

was twice less frequent in childhood-onset CD. These data further indicate an increased severity of childhood-onset CD. Some pediatric studies had already shown a trend of severe disease in childhood but without comparing these patients to adults.[2,13] The increased severity of CD at younger age may in part be related to genetic factors. Indeed, a family history of IBD is more frequent in CD diagnosed early in life,[22,23] which was also observed in our study. Another explanation may be due to a more widespread extent of lesions on proximal small bowel in young patients.[9] In order to avoid differences of severity due to disease location, patients were matched for initial disease location. However, we cannot exclude that during disease course, in contrast to adults,[15] lesions extend more in childhood-onset CD and contribute to the increased severity. Furthermore, one can hypothesize that age of the onset of the disease can trigger the intensity of the gut immune response. Young age is also the time when the Peyer's patches and lymphoid follicles of the small intestine are at their greatest number and probably at their greatest activity.[24] This may contribute to a more severe form of the disease at a young age.

Another important factor that has to be taken into account is the fact that initial management of CD may differ between children and adults. Thus, it appears difficult to assess severity of disease solely based on treatment regimen. For instance, given the major growth retardation in the majority of children with CD, enteral nutrition is considered first-line therapy[25,26] in order to avoid steroid use, and surgery is postponed whenever possible. It is also recognized that the use of immunomodulators increased steadily in adults during the 1990s,[17] whereas pediatricians tended to be more reluctant to prescribe them before 2000 and the demonstration of their efficacy by Markowitz et al.[27] Despite the fact that our cohort was set up before 2000, childhood-onset CD patients received azathioprine earlier in disease course. Finally, despite differences in strategy management, in our study childhood-onset CD displayed a more active disease course and received more aggressive therapy, suggesting more severe disease in this group.

Our data on height and weight of childhood-onset CD patients confirm data from the literature.[5,28,29] In our study the difference in height was small (3 cm), but we compared patients with a lag time of 20 years. Thus, it is likely that the difference observed would have been more important if childhood-onset CD patients were compared with patients of similar age. One can hypothesize that a significant difference was observed only in men because in this population CD occurs before the onset of puberty and decreases pubertal growth velocity,[5,23] while in women puberty and growth are completed at the beginning of the disease.

In conclusion, when comparing childhood- to adult-onset CD, a more severe disease course is observed in patients with childhood-onset forms, as documented by an increased disease activity index and an earlier exposure to major postsurgical sequelae. This increased severity phenotype is observed despite an increased immunomodulator use irrespective of disease location. These data suggest that

childhood-onset CD is most often associated with an intrinsic severe phenotype. An aggressive therapeutic approach should be considered in these patients.

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