

# Long-term prognosis of early-onset Crohn's disease diagnosed in childhood or adolescence

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Long-term follow-up data on Crohn's disease diagnosed before 20 years of age is limited. Mortality, intestinal malignancy and the need for resection were assessed in 224 patients with early-onset disease (96 males, 42.9%; 128 females, 57.1%). Mean follow-up was 12.2 years; more than 50% of patients were seen for over 10 years (almost 10% for over 25 years). Most patients were diagnosed from ages 13 to 19 years, rather than in childhood. Ileocolonic disease was most common (128 of 224; 57.1%), while upper tract involvement (42 of 224; 18.8%) was frequent. Complex disease with strictures (28.6%) or penetrating complications (46.4%) was common. To date, one patient with early-onset disease died from a drug overdose and one developed rectal cancer, but epithelial dysplasia has not been reported in endoscopic biopsies or resected intestine. One or more intestinal resections were required in 126 patients (56.3%; 58 males and 68 females). More than one resection was needed in 52 patients (23.2%). The mean time from diagnosis to first resection was 4.2 years and from first to second resection was 6.6 years, with most resections required in the first two years. Most patients who needed one or more resections had ileocolonic disease and had complex stricturing or penetrating disease. Information on long-term follow-up of early-onset Crohn's disease is crucial to avoid the direct extrapolation of adult data to children and adolescents.

**Key Words:** *Crohn's disease; Clinical behaviour of Crohn's disease; Granulomatous colitis; Natural history of Crohn's disease; Vienna classification*

Earlier studies, mainly from pediatric centres in the United States and Europe (1-9), but also Canada (10,11), have described the clinical features and prognosis of Crohn's disease diagnosed in childhood or adolescence. Although patient numbers have been limited and durations of direct pediatric physician follow-up have been short, most features typical of adult-onset disease were seen. The disease more commonly affected adolescents than children, but diagnosis even before five years of age has been recorded (5,7,12-14). Despite its chronic, often indolent nature, mortality has been low. Although significant morbidity, particularly growth retardation, has been recorded, recent studies (15) have suggested that the deficit in adult height after the early-onset of Crohn's disease may not be significant.

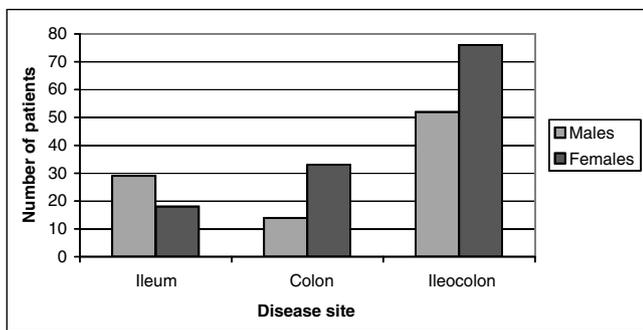
Crohn's disease is known to be phenotypically heterogeneous, involving different sites along the length of the gastrointestinal tract. Recent attention has focused on defining

## Pronostic à long terme de la maladie de Crohn chez les enfants et les adolescents

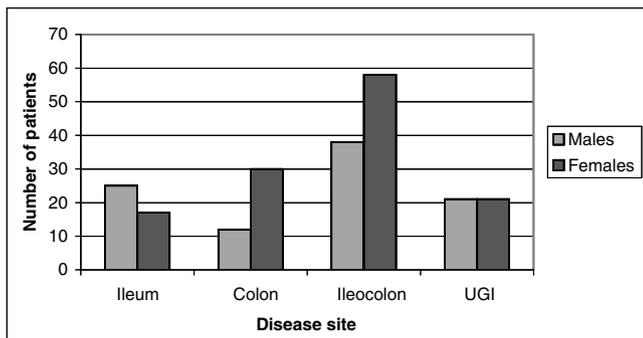
Il existe peu de données sur le suivi à long terme de la maladie de Crohn diagnostiquée avant l'âge de 20 ans. Nous avons donc évalué la mortalité, les affections malignes de l'intestin et les résections chez 224 patients (96 hommes, 42,9 %; 128 femmes, 57,1 %) atteints d'une maladie précoce. La durée moyenne du suivi était de 12,2 ans, et plus de 50 % des patients faisaient l'objet de suivi depuis plus de 10 ans (plus de 25 ans dans presque 10 % des cas). Le diagnostic a été posé, chez la plupart des patients, entre 13 et 19 ans, plutôt que durant l'enfance. L'atteinte iléocolique était très fréquente (128 sur 224; 57,1 %), suivie d'une atteinte du tube digestif supérieur (42 sur 224; 18,8 %). Les maladies complexes, accompagnées de sténoses (28,6 %) ou de perforations (46,4 %), n'étaient pas rares. Jusqu'à maintenant, un patient atteint d'une maladie précoce est mort d'une surdose de médicament et un autre présente un cancer du rectum, mais on n'a observé aucune dysplasie épithéliale dans les biopsies endoscopiques ou les résections de l'intestin. Il a été nécessaire de recourir à une ou plusieurs résections de l'intestin chez 126 patients (56,3 %; 58 hommes et 68 femmes). Plus d'une résection a été pratiquée chez 52 d'entre eux (23,2 %). Le temps moyen écoulé entre le diagnostic et la première résection était de 4,2 ans et entre la première et la deuxième, de 6,6 ans, bien que la plupart des résections aient été effectuées au cours des deux premières années. La plupart des patients qui ont subi une ou plusieurs résections présentaient une atteinte iléocolique, accompagnée de sténoses ou de perforations complexes. Il est crucial de recueillir des données sur le suivi à long terme de la maladie de Crohn précoce afin d'éviter l'extrapolation directe des données, des adultes aux enfants et aux adolescents.

more homogeneous patient groups based on clinical characteristics such as disease location or behaviour, as well as seromarkers (eg, anti-*Saccharomyces cerevisiae* antibodies and antineutrophil cytoplasmic antibodies). Studies using a modern schema of classification (16) demonstrated that Crohn's disease was female-predominant, occasionally familial and characterized by stricturing and penetrating clinical complications (17-19). Recently, these adult phenotypical features were also recorded in early-onset or pediatric Crohn's disease (20).

Several factors noted elsewhere (7), however, have made long-term evaluation of early-onset Crohn's disease difficult, including early difficulties in differentiation from ulcerative colitis, follow-up issues associated with transition to specialist adult care, and a tendency, especially during late adolescence, for increased mobility due to educational and employment requirements. Because long-term studies in pediatric patients with Crohn's disease are limited, data based on adult-onset



**Figure 1)** Disease location for male and female patients with early-onset Crohn's disease



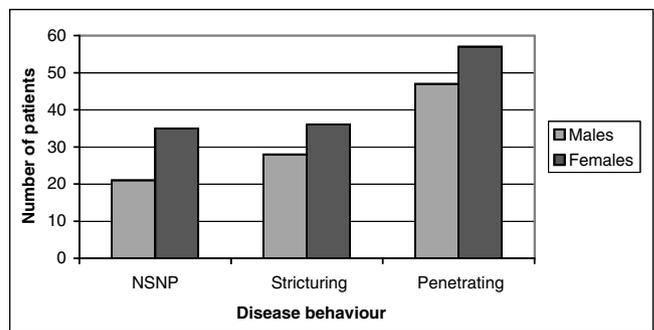
**Figure 2)** Disease location in early-onset Crohn's disease based on the Vienna classification (16,20). In this schema, the disease is classified as disease in the upper gastrointestinal (UGI) tract irrespective of disease occurring in the ileum or colon

Crohn's disease may be extrapolated to address long-term concerns, particularly in relation to prognosis. Using a modern classification schema (16), the present study explored specific long-term issues related to mortality, malignancy and the requirement for intestinal resection in 224 patients with early-onset disease who were diagnosed in childhood or adolescence, and seen directly over more than two decades.

## METHODS

### Definition and inclusions

The patients were derived from an established and prospectively and consecutively accumulated clinical database (now containing over 1000 patients with Crohn's disease), evaluated and directly treated by the investigator; mean patient follow-up period was over 10 years (17-20). In an earlier published report (17), this patient database was noted to be female-predominant (56.1%) with 84.4% diagnosed before 40 years of age. In addition, disease was observed to be localized to the ileum in 25.3%, the colon in 27.2%, the ileocolon in 34.6% and the upper gastrointestinal tract, despite disease involvement elsewhere, in 13.1%. Finally, disease behaviour was classified as stricturing in 33.6% and penetrating in 37.2%. Patients were selected for the present study if their diagnosis was defined before 20 years of age (20). The cohort that emerged included 224 patients, comprising 96 males (42.9%) and 128 females (57.1%). The mean duration of follow-up for the entire cohort was 12.2 years (males 12.7 years; females 11.8 years), with over 50% of patients followed for more than 10 years, and almost 10% of patients with data over 25 years (20). Statistical analyses were performed using the Student's *t* test or  $\chi^2$  test.



**Figure 3)** Disease behaviour in early-onset Crohn's disease, including nonstricturing, nonpenetrating (NSNP) disease; stricturing disease and penetrating disease

### Definition of early-onset Crohn's disease

Male and female patients were classified based on a prior schema developed elsewhere (16) and applied previously to this Crohn's disease database (17-20). For the purposes of the present study, modification of this schema was necessary for age at diagnosis because this classification does not specify a category for specific age groups younger than 40 years of age. Information for the present study, therefore, was restricted to age at diagnosis younger than 20 years. Other defining features were used including location of disease, defined as the maximal extent of disease or disease at the first resection (eg, L1, ileum, possibly involving cecum; L2, colon; L3, ileocolon; and L4, upper gastrointestinal tract regardless of other disease sites), and disease behaviour (eg, B1, nonstricturing and nonpenetrating; B2, stricturing; and B3, penetrating). In this classification, disease is defined as B3 if, at any time during the course of the disease, intra-abdominal or perianal fistula, perianal ulceration, inflammatory mass or abscess have developed, even if a co-existing stricture is present. In contrast to the definition of disease location, the definition of disease behaviour in this modern schema has no specific time limit. In the present study, disease behaviour was defined in a cumulative fashion as the most recent patient encounter during the past three years. Results of a comparative study for early-onset compared with adult-onset disease followed for similar periods have been recently published elsewhere (20).

This early-onset or pediatric Crohn's disease cohort was defined as female-predominant (57.1%) with the majority of patients first diagnosed during adolescence (13 to 19 years of age, inclusive), rather than childhood (younger than 13 years of age). Figure 1 schematically shows the classical sites of disease involvement being localized to ileum in 21% (males 30.2%; females 14.1%), colon in 21.0% (males 14.6%; females 25.8%) and, most often, ileocolon in 57.1% (males 54.2%; females 59.4%) ( $P < 0.05$ ). Upper gastrointestinal tract involvement, regardless of disease in the ileum or colon, was present in 18.8%. Figure 2 shows this resultant classification-based 'redistribution' of disease, using this modern Vienna schema solely for early-onset Crohn's disease (16,20). Figure 3 schematically shows clinical behaviour of early-onset disease being classified as complex disease in 75.0%, with stricturing complications in 28.6% (males 29.2%; females 28.1%) and penetrating complications in 46.4% (males 49%; females 44.5%).

### Medications and parenteral nutritional support

Further defining features were tabulated for this early-onset disease cohort. Table 1 lists different treatments used over more than two decades. Individual 5-aminosalicylate products or administration route for steroid preparations were not specified.

Immunosuppressive agents included azathioprine, 6-mercaptopurine, cyclosporine and methotrexate. A biological agent (eg, infliximab) was provided through a clinical trial in another hospital. Use of parenteral nutrition was recorded, but specified for home use, if required for nutritional support before or after intestinal resections. For percentages of males and females, medications were similar with a trend towards increased in-hospital total parenteral nutrition use in females. Compared with earlier data (17), medications were similar in early-onset disease except for a higher percentage of patients treated with steroids (eg, overall Crohn's disease database, 53.1%).

For the present study, comparisons were done between patients not requiring an intestinal resection and those requiring one or more intestinal resections. Mean ages at diagnosis for each group (no resection, one resection and multiple resections) were 16.3, 16.0 and 15.5 years, respectively, and were not statistically significant.

Familial disease (defined as confirmed first degree relatives with Crohn's disease) (18) for each group were 10.2%, 10.8% and 9.6%, respectively, and were not statistically significant. The prevalence of use of specific medications was also similar, including the percentage in each group treated with steroids, which was 70.4%, 71.6% and 73.1%, respectively, and not statistically significant.

### Recurrence and resection

Recurrence was defined in the present study as a further intestinal resection, rather than recurrent symptoms or recurrent radiological or endoscopic imaging changes. For each patient requiring another intestinal resection, durations of follow-up after the first and subsequent resections were recorded. To further clinically define the cohort being evaluated, pathological reports on resected intestinal specimens were also reviewed for reported detection of granulomas. In this cohort, granulomas were reported in 38.9% of all surgically resected specimens, including 31.1% of patients having one intestinal resection and 50.0% of those having more than one intestinal resection.

## RESULTS

### Malignancy and mortality

Only a single male with early-onset disease among these 224 patients developed an intestinal malignancy. He was initially diagnosed with Crohn's disease at 17 years of age in 1977. Endoscopic and radiological studies defined ileocolonic involvement. He was subsequently treated with different 5-aminosalicylate preparations, including sulfasalazine and eventually metronidazole, but no corticosteroids or immunosuppressive agents. He required an ileocolonic resection in 1980 for a localized ileal perforation proximal to a strictured ileal segment. Ileal and colonic ulcerations were present but granulomas were not detected in the resected intestine. Later, three colonoscopies with multiple ileal and colonic biopsies over the course of two decades showed only patchy inflammatory mucosal changes without granulomas. No dysplasia was detected. In 2003, he developed an anorectal stricture due to a low lying rectal adenocarcinoma and required an abdominoperineal resection.

To date, no patient with early-onset Crohn's disease has developed a myeloid or lymphoid malignancy, and all colonoscopic biopsies, either from macroscopically normal or abnormal intestine, have not demonstrated dysplasia. In addition, dysplasia has not been reported in resected intestine.

**TABLE 1**  
Medications used in early-onset Crohn's disease

Drug or treatment	Males n (%)	Females n (%)
5-aminosalicylate	70 (72.9)	96 (75.0)
Steroids	65 (67.7)	95 (74.2)
Antibiotics		
Metronidazole	33 (34.3)	50 (39.1)
Ciprofloxacin	13 (13.5)	11 (8.6)
Immunosuppressants		
Azathioprine	11 (11.5)	11 (8.6)
6-mercaptopurine	10 (10.4)	16 (12.5)
Cyclosporine	1 (1.0)	2 (1.6)
Methotrexate	1 (1.0)	4 (3.1)
Biological agents		
Infliximab	2 (2.1)	1 (0.8)
TPN in hospital	22 (22.9)	44 (34.4)
TPN in home	3 (3.1)	5 (3.9)

TPN Total parenteral nutrition

These findings contrast with earlier reported results on myeloid, lymphoid or intestinal malignancies in adults with Crohn's disease from the University of British Columbia hospital with a similar duration of follow-up (21). In that report, the estimated overall rate for myeloid and lymphoid malignancies was 0.5% and the estimated overall rate for intestinal malignancies was 1% (21). In addition, one patient with Hodgkin's disease, initially diagnosed at 10 years of age, was not included in the present evaluation of early-onset disease because her diagnosis of Crohn's disease was only established after 20 years of age.

Finally, to date, only one female, initially diagnosed at 15 years of age, and then followed directly by the investigator for 24 years, died following a suicidal drug overdose.

### Intestinal resections

One or more intestinal resections were required in 126 of 224 patients (56.3%) with early-onset disease, including 58 of 96 males (60.4%) and 68 of 128 females (53.1%). These percentages for intestinal resection all exceeded the previously recorded rate of 44.1% for an intestinal resection for a largely adult group from this hospital (17) ( $P < 0.05$ ). In this early-onset group, more than one intestinal resection was required in 52 of 224 (23.2%), including 24 of 96 males (25.0%) and 28 of 128 females (21.9%). Indeed, three or more intestinal resections were required in 21 of 224 (9.4%).

After diagnosis of early-onset Crohn's disease, mean time to the first intestinal resection was 4.2 years (range to 20 years). For males, mean time to the first resection was 4.2 years (range to 20 years), and for females, 4.1 years (range to 19 years). After the first resection, mean time to the second resection was 6.6 years (range to 25 years). For males, mean time to the second resection was 6.7 years (range to 23 years), and for females, 6.6 years (range to 25 years).

Table 2 further shows males and females with early-onset disease who required an intestinal resection for defined periods from the time of diagnosis to that of the first resection. As shown, for both sexes, the first intestinal resection was performed within the first two years after diagnosis in approximately 50%. Table 3 also shows the number of males and

**TABLE 2**  
Time from diagnosis to first resection

Time	Males (n=58) n (%)	Females (n=68) n (%)
0 to 2 years	25 (43.1)	35 (51.5)
3 to 5 years	15 (25.9)	14 (20.2)
6 to 10 years	13 (22.4)	12 (17.6)
11 to 20 years	5 (8.6)	7 (10.3)

**TABLE 3**  
Time from first resection to second resection

Time	Males (n=24) n (%)	Females (n=28) n (%)
0 to 2 years	8 (33.3)	9 (32.1)
3 to 5 years	7 (29.2)	5 (17.9)
6 to 10 years	5 (20.8)	9 (32.1)
11 to 20 years	3 (12.5)	4 (14.3)
Over 20 years	1 (4.2)	1 (3.6)

**TABLE 4**  
Disease location with single or multiple resections

	Males			Females		
	NR* n (%)	OR n (%)	MR n (%)	NR* n (%)	OR n (%)	MR n (%)
Ileum	14 (36.8)	11 (32.4)	4 (16.7)	8 (13.3)	5 (15.0)	4 (14.3)
Colon	10 (26.3)	4 (11.8)	0	29 (48.3)	4 (10.0)	0
Ileocolon	13 (34.2)	19 (55.9)	20 (83.3)	22 (36.7)	30 (75.0)	24 (85.7)

\*In the nonresected (NR) groups, there were also two patients with early-onset disease (one male, one female) who had isolated upper gastrointestinal tract disease without ileal or colonic involvement. MR Multiple resections; OR One resection

females who required a second intestinal resection for defined periods after the first resection. The second intestinal resection was also required within two years in approximately one-third of both male and female patients.

Table 4 compares disease location in males and females who did not require an intestinal resection with those who required one or multiple intestinal resections. For both males and females, most early-onset Crohn's disease with ileocolonic involvement required at least one, and usually multiple intestinal resections, while both males and females with only localized colonic disease were less likely to require an intestinal resection ( $P < 0.05$ ). Table 5 shows the data redistributed using the modern Vienna system (16). With this schema, the disease is categorized as upper tract in type even if it is also detected in ileum or colon. Even with this modification, for both males and females, most who eventually required an intestinal resection had ileocolonic involvement ( $P < 0.05$ ).

Table 6 compares clinical behaviour of males and females with early-onset Crohn's disease, defined on the basis of the modern Vienna schema (16), in patients having no intestinal resection compared with those having one or multiple intestinal resections. More resected patients could be classified as having complex disease with either strictures or penetrating disease complications ( $P < 0.05$ ).

**TABLE 5**  
Disease location using the Vienna classification system and resections

	Males			Females		
	NR n (%)	OR n (%)	MR n (%)	NR n (%)	OR n (%)	MR n (%)
Ileum	13 (34.2)	11 (32.4)	1 (4.2)	7 (11.7)	6 (15.0)	4 (14.3)
Colon	9 (23.7)	3 (8.8)	0	28 (46.7)	4 (10.0)	0
Ileocolon	10 (26.3)	14 (41.2)	14 (58.3)	18 (30.0)	23 (57.5)	17 (60.7)
UGI	6 (15.8)	6 (17.6)	9 (37.5)	7 (11.7)	7 (17.5)	7 (25.0)

MR Multiple resections; NR No resection; OR One resection; UGI Upper gastrointestinal tract involvement regardless of involvement elsewhere

**TABLE 6**  
Disease behaviour and intestinal resection

	Males			Females		
	NR n (%)	OR n (%)	MR n (%)	NR n (%)	OR n (%)	MR n (%)
NSNP	18 (47.4)	2 (5.9)	1 (4.2)	30 (50.0)	5 (12.5)	0
Strict	12 (31.6)	11 (32.4)	5 (20.8)	11 (18.3)	14 (35.0)	11 (39.3)
Penet	8 (21.1)	21 (61.8)	18 (75.0)	19 (31.2)	21 (52.5)	17 (60.7)

MR Multiple resections; NR No resection; NSNP Nonstricturing and nonpenetrating; OR One resection; Penet Penetrating; Strict Stricturing

## DISCUSSION

The present study focused on an exploration of specific disease end points traditionally used as clinical indicators of long-term prognosis in Crohn's disease, but applied to early-onset disease diagnosed during childhood or adolescence. These included malignancy and mortality as well as the requirement for intestinal resection. As anticipated, the results show that both early malignancy and mortality are rare, each being noted only in single patients (eg, rectal cancer, suicidal drug overdose), around 40 years of age and beyond. These observations are consistent with the results in other studies on clinical features of pediatric Crohn's disease that have failed to record superimposed or complicating intestinal malignancies (5-7). Indeed, colorectal cancer complicating early-onset Crohn's disease has been rarely reported, and has been considered to be more likely related to another occult or underlying genetically-based disorder (eg, Li-Fraumeni syndrome) than Crohn's disease per se (22).

While not systematically examined in the present study, regular colonoscopic screening programs for epithelial dysplasia (or invasive neoplasia) appear not to be indicated in children or adolescents with Crohn's disease. Not a single patient in this cohort of 224 patients followed for a prolonged period by a single clinician had epithelial dysplasia recorded in endoscopic biopsies or surgically resected specimens, including the sole patient who eventually developed colorectal cancer. Epithelial dysplasia in Crohn's disease has been recorded elsewhere in the small and large intestine, leading others to hypothesize that the so-called 'dysplasia-carcinoma sequence' may occur in Crohn's disease (23). Although very logical, data to support an endoscopic surveillance approach are limited in Crohn's disease, and are largely based on a single study conducted in an older adult population (24). Indeed, most cases of carcinoma in adults with Crohn's disease, even from large tertiary care settings, were detected only incidentally during surgical treatment (25). Evidence providing support for routine

endoscopic surveillance in pediatric Crohn's disease is lacking and should not be recommended based on the limited data from adult populations.

The present study also evaluated the role of clinical characteristics, based on a modified Vienna schema for early-onset or pediatric Crohn's disease (16,20), and the likelihood for later intestinal resection(s). In this evaluation, the majority of males and females (56.3%) required at least one intestinal resection during the prolonged period of follow-up into adulthood. This exceeds the recorded frequency of 44.1% in a larger database (16), now with over 800 having adult-onset disease. These results are consistent with a prior report of a higher frequency of surgical treatment in early- versus late-onset disease over 40 years of age (26) and also provide predictive data for anticipated intestinal resection after diagnosis of Crohn's disease. The data here indicate that an intestinal resection, if required, will usually be performed within two years of the initial diagnosis. Moreover, if a second resection is required, this is also frequently done within two years following the first resection. While it was not possible to evaluate the effects of therapy on the natural history of Crohn's disease before resection in the present study, future investigations focused on new therapeutic drugs and biological agents should distinguish early-onset from adult onset disease.

The present study in early-onset Crohn's disease also explored the effects of disease location and clinical behaviour on rates of intestinal resection. In this investigation, disease

located in the ileocolonic region and characterized as complex disease with intestinal strictures or, more frequently, penetrating (or perforating) disease complications were independent risk factors that often predicted a later intestinal resection. These observations confirm the clinical experience that children or adolescents with Crohn's disease are more likely to require surgical treatment relatively soon after diagnosis if disease is clinically complicated with stricture formation or penetrating disease complications, such as the development of an abscess or a fistulous tract. Further studies are needed to define other prognostic factors that might predict the need for earlier surgical treatment of Crohn's disease.

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