The Natural History of Crohn Disease in Children

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James F. Markowitz

Introduction

Determining the natural history of Crohn disease involves the consideration of a number of different factors: disease activity over time, frequency of complications, the need for surgery, and the risk of disease recurrence following both medically induced and surgically induced remission. In children, evaluation of the natural history also must include the effects of Crohn disease on growth and development and on quality of life.

The true natural history of Crohn disease remains largely unknown, however, primarily because there are virtually no data describing the long-term course of untreated children or adults with this illness. The data that does exist arise from early clinical experience treating patients with corticosteroids and 5-aminosalicylate medications, and from a small number of placebo-controlled treatment trials. These data document that the natural history of Crohn disease is one associated with significant morbidity. As a consequence, one of the goals of current therapy includes improving the natural history of the disease. It is yet not clear, however, whether current therapy including the use of immunomodulatory or biologic medications or the introduction of these agents earlier in the course of treatment, in fact, accomplishes this goal.

Disease Activity

Spontaneous remission in the absence of specific treatment can occur in Crohn disease. Two early adult trials, the National Cooperative Crohn's Disease Study (NCCDS) [1] and the European Cooperative Crohn's Disease Study (ECCDS) [2], included placebo treatment arms enrolling a total of less than 300 adult subjects. Among the 135 subjects with active disease at entry into the two trials, 26–42% achieved clinical remission after 3–4 months of placebo treatment, and 18% in both studies remained in clinical remission at 1 year [1, 2]. Prolonged spontaneous remission therefore appears to occur in only a small number of adults with Crohn disease. However, in the NCCDS, among the subgroup of 20 subjects with active disease who achieved clinical remission by 17 weeks, 75% remained in remission at 1 year, and 63% at 2 years [1]. Similarly, among the 153 subjects in the NCCDS and ECCDS who had inactive disease when randomized into the placebo arms of a maintenance study, 52–64% remained in remission at about 1 year and 35–40% at about 2 years [1, 2].

No comparable data from untreated or exclusively placebo treated children exist. However, in children with moderate-severe disease activity who achieve remission after a course of prednisone, the likelihood of prolonged remission without ongoing therapy appears lower than in adults. Newly diagnosed children randomized to the control arm of a multicenter trial received prednisone for induction of remission and were then maintained only on placebo [3]. One year following the course of corticosteroids, only 43% remained in remission. Similarly, 95% of a cohort of Italian children maintained on mesalamine following an 8-week course of corticosteroids relapsed by 1 year [4].

Periods of active Crohn disease continue to be a problem beyond the first year after diagnosis. Disease activity over time has been described in a report derived from a large population-based inception cohort of patients with inflammatory bowel disease diagnosed and treated in Copenhagen County, Denmark between 1962 and 1987 [5]. While useful, the data describing the course of pediatric Crohn disease in this study are based on observations of only 23 children. At diagnosis, 82.6% had disease activity characterized as moderate to severe. In each of the succeeding 9 years, only about 50% of the cohort was characterized as inactive during any given year, while roughly 20–35% had periods of high disease activity despite treatment (Fig. 7.1) [6].

J.F. Markowitz, MD (✉)
Department of Pediatrics, Division of Pediatric Gastroenterology and Nutrition, Steven and Alexandra Cohen Children's Medical Center of New York, 269-01 76th Avenue, New Hyde Park, NY 11040, USA
e-mail: jmarkowi2@nshs.edu

P. Mamula et al. (eds.), *Pediatric Inflammatory Bowel Disease*,
DOI 10.1007/978-1-4614-5061-0_7,

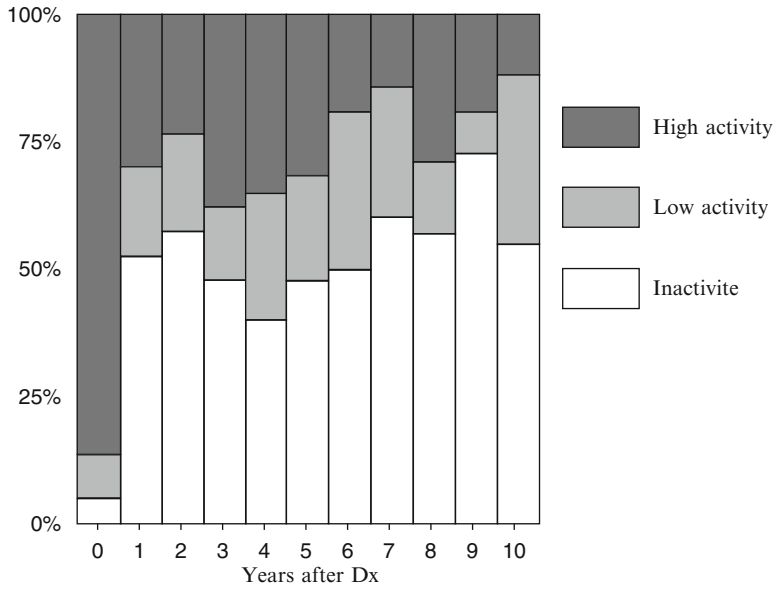

Fig. 7.1 Yearly Crohn disease activity over the first 10 years after diagnosis in a Danish population of children diagnosed prior to 15 years of age. Data from Langholz et al. [5] [figure redrawn]

Observations in the larger, primarily adult onset cohort from the same geographic area revealed that individual patients had different patterns of clinical activity over time: some experienced frequent relapses, some only occasional relapses, and others had prolonged periods of disease quiescence [6]. In this cohort, relapse in any given year after diagnosis increased the risk of relapse in the following year. Relapse rate in the first year after diagnosis also correlated with relapse rate in the next 5–7 years. A review of North American experience revealed similar patterns of disease, with most patients having a chronic intermittent disease course, but 13% of patients having an unremitting disease course and only 10% experiencing a prolonged remission [7].

Evolution of Disease Phenotype

Disease location is not fixed over time. In a recent report from Scotland, at diagnosis extensive disease including the ileum, colon, and upper GI tract (disease location characterized as L3 + L4 by the Montreal classification [8]) was found in 31% of children [9]. However, among a subgroup of 149 children with less extensive disease at diagnosis who were followed at least 2 years after diagnosis, extension of CD was noted in 39% [9].

Disease behavior also evolves over time. At initial diagnosis, the vast majority of children have an inflammatory disease phenotype. However, as time goes on, an increasing proportion expresses a changing phenotype, characterized as either stricturing or penetrating. This has been documented clearly in data derived from the pooled observations from three multicenter North American pediatric IBD registries [10]. Among 796 children followed prospectively from diagnosis, 96 (12%) presented with a stricturing or penetrating CD phenotype. Among the 700 who had an inflammatory phenotype at presentation, 140 (20%) developed stricturing or penetrating disease after a mean of 32 months of follow-up [10], a finding strikingly similar to the 24% rate of complicated CD behavior described after 4 years in a pediatric study from Scotland [9]. Similar observations over extended periods of time have been reported in population-based studies in adults from both France [11] and New Zealand [12] (Fig. 7.2). In the latter study, a comparison of 630 subjects with adult-onset disease and 85 children diagnosed before age 17 years revealed no difference in the rate of progression from inflammatory to either stricturing or penetrating disease phenotype [12].

Racial differences may affect the frequency of complicated CD, as a study from Baltimore has demonstrated more frequent stricturing and penetrating disease in black children compared to white children seen in the same university-based practice [13]. The risk for phenotypic change may also be associated with the presence of specific genetic allelic variants. For instance, patients with NOD2/CARD15 variants appear to be at increased risk for fibro-stenosing complications [14, 15], while those with abnormalities in the IBD5 gene may be more likely to develop perianal fistulae [16]. Children at risk for stricturing or internal penetrating complications have also been shown to be more likely to have increased immune responses to microbial antigens, characterized by the presence of high titer antibodies such as anti-ompC and anti-I2 [10, 17].

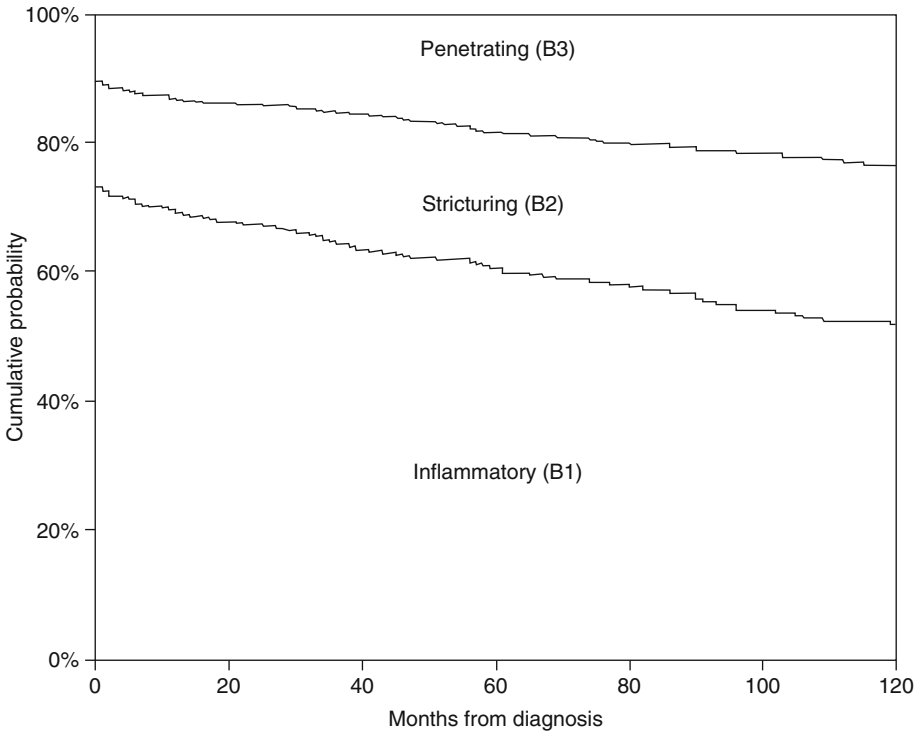

Fig. 7.2 Change in Crohn disease behavior over time in a population-based study from New Zealand. Reproduced with permission from Nature Publishing Group; Macmillan Publishers Ltd [12]

Growth

For a significant subgroup of children with Crohn disease, growth impairment is an important characteristic of the disease's natural history. While acute weight loss commonly is present in children with both ulcerative colitis and Crohn disease, impairment in linear growth is primarily a problem in the latter condition. At the time of initial diagnosis, about a third of children with Crohn disease has already dropped two or more major growth channels from their preillness growth percentiles [18, 19]. More dramatically, 88% have delayed height velocity at diagnosis [20]. Over time, periods of significantly impaired growth can be seen in about 60% of children and adolescents [19]. While catch-up growth is often possible, 7–35% of children diagnosed during the 1970s and 1980s had final adult heights that were significantly shorter than expected [19]. As a group, young adults who develop Crohn disease as children have adult heights skewed towards the lowest percentiles. In reports from both Chicago and New York, ~50% of young adults with childhood onset Crohn disease have final adult heights less than the 10% for the general population, and ~25% have adult heights less than the 5% [18, 19]. While therapies including enteral nutrition [21] and infliximab [22, 23] have improved growth in the short to medium term, current therapies have not yet been demonstrated to provide a long term reversal of growth impairment.

Corticosteroid Dependence

An important characteristic of Crohn disease in children as well as adults is the tendency to develop corticosteroid dependence. Population-based studies in adults from both Olmsted County, MN [24] and Copenhagen County, Denmark [25] demonstrate similar findings. These studies document that acute response to corticosteroid therapy in adults with Crohn disease is reasonably good (complete remission in 48–58%, partial remission in 26–32%, and no response in 12–20%). However, long-term response is less optimal, with rates of corticosteroid dependence of 28–36% at 1 year [24, 25].

A similar risk for corticosteroid dependence is evident in children. As in adults, acute response to a course of corticosteroids is good. In data derived from a multicenter North American observational registry, among newly diagnosed children with moderate-severe Crohn disease activity treated with corticosteroids, 60% have a complete and 24% a partial clinical response by 3 months after initiation of treatment [26]. However, despite concomitant use of immunomodulators in many of these children, 31% are corticosteroid dependent at 1 year. In fact, without infliximab, only 46% of the children in this study maintained a corticosteroid free remission to 1 year following an initial course of corticosteroids [26].

Surgery

The need for surgery represents another important aspect of the natural history of Crohn disease in children. Table 7.1 summarizes published rates for surgery in children from a variety of different countries. Data from Denmark estimate a mean yearly operation rate of approximately 13%. The cumulative probability of surgery in this Danish cohort at 20 years was estimated to be 47% [5]. A more recent multicenter pediatric experience from the USA estimates the cumulative incidence of surgery to be 6% at 1 year, 17% at 5 years, and 28% at 10 years after diagnosis [31]. Similarly, a pediatric study from Scotland noted resection rates of 20% at 5 years and 34% at 10 years [9]. The presence of variant NOD2/CARD15 alleles appears to increase the risk for surgery, presumably due to the known association of these genetic polymorphisms with the development of fibrostenotic ileal disease [14, 15]. The presence of anti-*Saccharomyces cerevisiae* antibodies also appears to be associated with increased risk for surgery [10, 31].

The effect of immunomodulatory therapy on the need for surgery remains an open question. An analysis from France evaluated a series of successive 5-year adult CD cohorts [32]. Although there was a significant increase in the use of immunomodulatory therapy over time, there was no associated change in the rate of surgery [32]. By contrast, multivariate analysis from a similar series of 5-year adult CD cohorts from the United Kingdom identified the early use of thiopurines (within 3 months of diagnosis) to be associated with a marked reduction in the rate of surgery [33].

The benefit of infliximab therapy in decreasing surgical rates is equally unclear. In a Spanish retrospective assessment of infliximab therapy used in a "step-up" fashion, no significant decrease in surgical rates could be identified in patients receiving infliximab compared to those not receiving the treatment [34]. However, other studies reach the opposite conclusion. For instance, in a study utilizing data from a combined Danish and Czech collaboration, surgical rates in adults 40 months after starting infliximab were 20–23% in infliximab responders compared to 76% in non-responders [35]. Similar findings in children have been reported, with surgical rates 50 months after starting infliximab of 10% in patients maintained on the biologic compared to 70% in infliximab failures [36].

Postoperative Recurrence

Although there are little hard data published to document clinical experience, following surgery, the natural history of Crohn disease is to recur both endoscopically and symptomatically. In retrospective adult studies, symptomatic recurrence of Crohn disease following so-called curative resection (complete resection of all visibly evident disease) is reported to be 20–30% within the first year after surgery, with increasing likelihood in each subsequent year [37]. One or more additional surgeries are required in 15–45% of adults within 3 years, 26–65% in 10 years, and 33–82% in 15 years [25]. Controlled trials document severe endoscopic recurrence after placebo treatment in 43–79% of adult subjects by 1 year after surgery and in 42–85% of subjects after 2 years [38–43].

In children, the overall rate of clinical recurrence is estimated to be 50% at 5 years after initial resection [29]. However, the site and extent of preoperative Crohn disease can affect the recurrence free interval, such that it is estimated that 50% of children with extensive ileocolitis recur within 1 year, compared to a 50% recurrence rate after 5 years in children with ileocecal disease, and a 50% recurrence rate after 6 years if preoperative disease is confined to the small bowel [29]. Additional risk factors for postoperative recurrence in children are summarized in Table 7.2.

Cancer Risk

Whether children with Crohn disease are at increased risk for malignancy over their lifetime is unknown. No data derived from a population with childhood onset Crohn disease have been reported. Studies in adults, however, suggest that Crohn disease patients do have an excess of malignancies compared to the general population. In a population-based cohort from the Uppsala region of Sweden, there was an increased relative risk of colorectal cancer of 2.5 (95% confidence interval 1.3–4.3) in patients with Crohn disease [46]. Duration of illness

Table 7.1 Surgical frequency in Crohn disease

Authors	# Children observed (period studied)	% Operated	% Permanent stomas
Farmer [27] (US)	522 (1955–1974)	67	NR
Ferguson [28] (UK)	50 (1968–1983)	78	30
Griffiths [29] (Canada)	275 (1970–1987)	32	2
Besnard [30] (France)	119 (1975–1994)	30	2
Langholz [5] (Denmark)	23 (1962–1987)	43	NR
Gupta [31] (US)	989 (1987–2003)	13	10

Table 7.2 Risk factors for postoperative recurrence in children

Authors	*N*	Ages (years)	Risk factors for recurrent Crohn disease
Griffiths [29] (Canada)	89	5.9–19	Effect of initial disease location on RFI: Extensive ileocolonic = 1 year Ileo/ileocecal = 5 years Small bowel = 6 years
			Effect of surgical indication on RFI: Specific intestinal indication (e.g., stricture, fistula) = 6 years Failed medical therapy = 1.7 years
			Effect of preoperative duration of disease on RFI: <1 year = 8+ years >1 year = 3–4 years
			No difference on RFI found for: age, pathologic features, pre-op bowel rest
Besnard [30] (France)	30	7.5–16.5	Multifocal disease preoperatively: 12/12 recurrences with upper GI or perianal disease
			No difference found for: age, preoperative disease duration, disease activity, extension, preoperative nutritional support, preoperative mesalamine or azathioprine
Baldassano [44] (US)	79	0.3–21	Effect of preoperative 6-MP on RFI: No preoperative 6-MP = 4.45 years Preoperative 6-MP = 1 year If 6-MP discontinued postoperatively, 5/6 relapse in 8 months If 6-MP continued postoperatively, 1/3 relapse at 2.5 years
			Effect of initial disease location on RFI: Colonic = 1.16 years Ileocecal = 4.36 years Colon/small bowel = 2.95 years
			No difference found for: age, race, gender, appendectomy, preoperative disease duration, indication for surgery, pathology

Table reprinted from Markowitz et al. [45]
RFI recurrence free interval

and gender did not affect risk, but those subjects with colonic disease had a greater risk of colorectal disease than those with only small bowel involvement. Of note, however, among those subjects with any colonic involvement diagnosed with Crohn disease before the age of 30 years, the relative risk of colorectal cancer increased to 20.9 (95% Confidence interval 6.8–48.7) [45]. By contrast, a similar population-based study from Denmark identified a relative risk of colorectal cancer of only 1.1 (95% confidence interval 0.6–1.9), and no risk differences were noted in different subgroups of patients [47]. A similar modest increase in colorectal cancer risk (1.9; 95% confidence interval 0.7–4.1) was found in a population-based study from Olmsted County, MN [48].

By contrast, the risk of small bowel cancer consistently appears increased in patients with Crohn disease. In part because the rate of small bowel cancer in the general population is very low (estimated to be 0.005% at 5 years and 0.03% at 25 years according to data cited in reference 48), the relative increased risk for small bowel cancers in Crohn disease patients is significantly elevated. In the Danish study cited earlier, the relative increased risk for small bowel cancer was 17.9 (95% CI 4.8–42) [47]. In Olmsted County, the relative risk was found to be 40.6 (95% CI 4.4–118) [35]. Duration of Crohn disease did not appear to influence risk of developing a small bowel cancer. Adenocarcinoma, carcinoid, leiomyosarcoma, and primary intestinal lymphoma have all been reported. The effect of age at Crohn disease onset on the risk of developing small bowel cancer has not been reported.

There may also be a slight increase in risk of developing lymphoma. Among 454 adults living in Olmsted County who developed Crohn disease between 1950 and 1993, 1 developed a non-Hodgkin's lymphoma, resulting in a slight increase in relative risk (2.4; 95% CI 0.1–13) compared to the general population [49]. In this report, however, the referral practice of the same group of investigators revealed that development of lymphoma was associated with treatment with immune modifiers in about 5% of cases [49]. A recent meta-analysis utilizing data from six studies estimates the risk of lymphoma in IBD patients treated with azathioprine or 6-mercaptopurine to be increased about fourfold (4.18; 95% CI 2.07–7.51) [50]. Infliximab may add an additional element of risk, especially for children and young adults, in whom the development of a hepatosplenic T-cell lymphoma has been described [51]. Whether these risks to children with

Crohn disease are due to the nature of the illness in children, their frequent need for potent immune modifier and biologic therapy, or both is not known.

Quality of Life

In addition to imposing significant physical morbidity, the natural history of Crohn disease in childhood imposes potentially dramatic psychosocial burdens as well. Health-related quality of life (HRQOL) scores, as measured by the IMPACT questionnaire (a validated, pediatric IBD health related quality of life questionnaire) [52] correlate with physician's global assessment of disease severity, such that children with moderate-severe activity have the poorest HRQOL scores [53]. Over the first year after diagnosis, age also appears to be an independent factor affecting HRQOL scores, with older children reporting poorer IMPACT scores [53]. While treatment results in significant improvement in IMPACT scores in the first year after diagnosis, it is unknown whether further improvements in HRQOL occur over time. Children frequently report being bothered by having a chronic illness, by having to undergo tests, and by feeling tired. Over time, they also report feeling that it is unfair that they have their illness, and that they experience problems revolving around having to keep their illness a secret from others [53].

Other studies have noted that children with Crohn disease experience frequent absences from school, that they frequently require home tutoring, and that they commonly cannot participate fully or at all in physical education classes [54, 55]. Children express fears concerning everyday childhood activities, schooling, and ability to get a job [56]. Fifty-seven percent of a cohort was reported to have had an absence from school of at least 2 months duration, and in this same cohort, 8% were involuntarily unemployed as young adults [57]. Similar impairments are described in adult Crohn disease populations, with 15% of a Danish population on disability by 15 years after diagnosis, 25% reporting some inability to work in any given year of follow-up, and 50% reporting 1 or more years during first decade of disease with at least some inability to work [6].

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