Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.1315

World J Gastroenterol 2009 March 21; 15(11): 1315-1318
World Journal of Gastroenterology ISSN 1007-9327

OBSERVATION

Hugh James Freeman, MD, FRCPC, FACP, *Series Editor*

Long-term natural history of Crohn's disease

Hugh James Freeman

Hugh James Freeman, Department of Medicine (Gastroenterology), University of British Columbia, Vancouver V6T 1W5, Canada
Author contributions: Freeman HJ contributed all to this paper.
Correspondence to: Dr. Hugh James Freeman, MD, FRCPC, FACP, Department of Medicine (Gastroenterology), University of British Columbia Hospital, 2211 Wesbrook Mall, Vancouver V6T 1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216 Fax: +1-604-8227236
Received: January 19, 2009 Revised: February 16, 2009
Accepted: February 23, 2009
Published online: March 21, 2009

Abstract

Crohn's disease is a chronic inflammatory granulomatous process that usually involves different sites in the intestinal tract. Genetic and environmental factors are thought to play a role in its etiology and pathogenesis. The disorder has a heterogeneous clinical expression and data from tertiary care settings have documented its female predominance, occasional familial nature, and high rate of stricture formation and penetrating disease. It may appear from early childhood to late adulthood, although over 80% are currently diagnosed before age 40 years, usually with terminal ileal and colonic involvement. Several studies have now shown differences in phenotypic clinical expression depending on the initial age at diagnosis, with pediatric-onset disease being more severe and more extensive with more involvement of the upper gastrointestinal tract compared to adult-onset disease. In addition, long-term studies from these tertiary care settings have documented that the disorder may evolve with time into a more complex disease with stricture formation and penetrating disease complications (i.e. fistula and abscess). Although prolonged remission with no evidence of inflammatory disease may occur, discrete periods of symptomatic and active granulomatous inflammatory disease may re-appear over many decades. Long-term studies on the natural history have also suggested that discrete events (or agents) may precipitate this granulomatous inflammatory process.

Key words: Natural history; Crohn's disease; Age-dependent phenotypes; Clinical behavior; Granulomatous inflammation

Peer reviewer: Dr. Cosimo Prantera, Chief, Head of Gastroenterology Unit Azienda Ospedaliera, S.Camillo-Forlanini, Circonvallazione Gianicolense 87, Roma 00152, Italy

Freeman HJ. Long-term natural history of Crohn's disease. *World J Gastroenterol* 2009; 15(11): 1315-1318 Available from: URL: http://www.wjgnet.com/1007-9327/15/1315.asp
DOI: http://dx.doi.org/10.3748/wjg.15.1315

INTRODUCTION

Crohn's disease is a chronic inflammatory granulomatous disorder that usually involves different sites along the length of the intestinal tract. Genetic and environmental factors are believed to play a role in its etiology and pathogenesis. As Crohn's disease is very heterogeneous in its clinical expression, working groups at the World Congress of Gastroenterology, held initially in Vienna and later in Montreal, have developed an evolving classification scheme[1,2]. An important goal has been to enumerate different phenotypic characteristics so that more homogeneous subgroups can be explored. Application to a specialist care clinical database noted a female predominance, occasional familial nature, and a high rate of stricture formation and penetrating disease[3-5].

The disorder seems to be life-long and may appear at almost any time from early childhood to late adulthood[1-3]. However, for most, the actual onset of the disease, or more precisely the age at diagnosis, is usually during the late teens and early twenties, and now, during the past two or three decades, over 80% of patients with Crohn's disease are diagnosed before the age of 40 years[3]. Moreover, the majority have involvement primarily of the ileum and colon, at least based on the most sensitive and modern imaging methods[1-3]. Finally, most specialists usually see late complicated disease, while early disease without stricture or fistula development may not be seen as often, particularly in specialist or tertiary-care centers.

DISEASE ONSET AND AGE AT DIAGNOSIS

Clearly, an appreciation for the natural history of Crohn's disease must depend, not on the age at diagnosis

defined by these classifications, but the actual time of onset of the disorder. These are obviously very different. Symptoms that eventually lead the patient to specialist referral include diarrhea, abdominal pain and weight loss, but these are not always universally present. Occasionally, only a single symptom, possibly abdominal pain, may be evident. In some, detection of an unexpected ileal inflammatory process at laparotomy for suspected appendicitis may be the first presentation. For others, extra-intestinal findings (e.g. arthopathic process or a skin disorder, such as erythema nodosum) may be present without significant intestinal symptoms. In some, symptoms have often been present for variable periods of time, even months or years, before a diagnosis is established. Also, in these, an event (or possibly an infectious agent) that initiated this destructive inflammatory process may no longer be detectable, having long left the patient. Indeed, multiple events (or agents) can conceivably generate this insidious inflammatory cascade that causes clinical symptoms and the appearance of a common end-pathological change labeled Crohn's disease. Even hypothetical genetic, microbiological and immunological factors that permit ongoing progression of this frustrating clinical disorder still require elucidation.

DISEASE LOCALIZATION, EXTENT AND BEHAVIOR

Most intriguing is the apparent predilection of the disease for the distal small intestine and proximal colon[3]. More extensive involvement of the small intestine and colon may occur[6], and the old adage that Crohn's disease can potentially involve any site "from mouth to anus (and probably elsewhere in the case of "metastatic" disease)" still holds true. Moreover, genetic factors may play a role in localization of the disease to different intestinal sites[7,8]. Further information, however, is clearly required on basic luminal and intestinal factors that play a role in localization of the disorder to specific sites along the gastrointestinal tract. Crohn's disease can occasionally occur in the upper gastrointestinal tract, usually with disease elsewhere in the ileum, colon, or both. The disorder may also occur only in the upper gastrointestinal tract without disease involvement elsewhere, albeit rarely[2,3]. Also, extensive jejunoileal involvement, evaluated over the long-term, illustrates a special subgroup of Crohn's disease that historically responds poorly to medication, which often leads to surgical treatment and long-term nutritional support[6]. New and developing biological treatment paradigms largely focused on reducing numerical indices in ileocolonic disease may have little impact on this subgroup, unless the severity and extent of the inflammatory process can be reduced.

Crohn's disease is a chronic, persistent and destructive disorder with distinct forms of clinical behavior that may also, in part, be genetically-based[9,10]. It also seems progressive, although the rate of progression may be altered or slowed, by the use of some therapy, such as steroids, antibiotics, or resective surgery, at least for a period of time. It appears that the disease begins as an inflammatory process that progressively develops over time to a more complex disease with stricture and fistula formation[11-13]. Once initiated, it is likely that numerous genetic and environmental factors play a role in regulating the rate of progression, but these are poorly understood. Moreover, the progression itself may not be linear but occur in a step-wise fashion with prolonged symptom-free periods over many decades[14].

Crohn's disease may also initially present as an already advanced and clinically complex disease with extensive or multiple jejunoileal strictures[6], sometimes even with free perforation of the small intestine, or alternatively, with large intra-abdominal inflammatory masses, sometimes with a deeply penetrating fistula (e.g. ileosigmoid fistula). In some, it has been hypothesized that recurrent disease may occur as a patterned clinical response, possibly related to specific genetic regulatory factors. For instance, recurrent stenotic events may result in a localized ileocecal resection, new erosions and ulcers in the neo-terminal ileum, and further stricture formation, recurrent obstructive symptoms and another resection[15]. Or, recurrent penetrating events with fistula and abscess formation may occur[15]. Classifying clinical behavior in Crohn's disease is difficult and may not be truly reflective of natural history as the rates of development of a complication, such as a stricture formation, may differ markedly, not only among patients, but even in the same patient during the disease course. Some may have either a rapidly progressive inflammatory process, or alternatively, a low grade sub-clinical process, possibly present for months, that suddenly becomes clinically expressed.

AGE-RELATED PHENOTYPIC EXPRESSION

Early historical studies have suggested that the phenotypic clinical expression of Crohn's disease differs substantially, depending on the age of initial diagnosis[16-20]. This age-dependent phenotypic clinical expression probably reflects the dynamic nature of the disorder[21]. Disease developing earlier in children and adolescents tends to be much more severe, often resulting in significant disease complications, including strictures or fistulae, or both[22-25]. It is also more extensive, often involving multiple sites in the small and large intestine, with a higher frequency of involvement of the upper gastrointestinal tract[22-25]. Comparative studies also show significant differences in clinical expression for children and adults[21,22], as well as the elderly[26]. Others have defined a difference in some immunoreactive characteristics of early-onset compared to late-onset Crohn's disease[27,28]. The hypothesis that a dysregulated immune response, likely affected by aging *per se* and leading to different phenotypic disease expressions of Crohn's disease, needs to be further elucidated.

CLINICOPATHOLOGICAL CORRELATIONS

Clinical and pathological correlations have been explored during the long-term clinical course of Crohn's disease. Some early historical descriptions have tended to avoid the possible temporal sequence of progression of pathological lesions and have focused on their prognostic significance[29,30]. However, more recent studies of their chronological sequence have suggested early small ulcers or granulomas with ongoing progression to later sinuses and strictures complicating large ulcers[31]. Later studies have also confirmed that this granulomatous inflammation may be a histopathological marker for an early phase of the inflammatory process in Crohn's disease, at least prior to development of fibrotic strictures and fistulous tracts[31]. Granulomatous inflammatory change has been documented in multiple biopsy or surgically resected specimens obtained over many decades[14]. Often, long intervals of relatively symptom-free disease are also evident[14]. This temporal pattern may indicate multiple initiating events in Crohn's disease with different rates of progression, or alternatively, granulomas may reflect ongoing active inflammation, even as subclinical or asymptomatic disease.

These studies have also suggested a geographic change in Crohn's disease with extended periods of time[32]. For instance, granulomatous ileal involvement was defined many years after initial colonic disease, and gastroduodenal disease occurred after ileocolic resection. If there were a single event that initiated this granulomatous inflammatory process, then different tissues along the length of the gastrointestinal tract may develop a granulomatous response at different rates, or alternatively, there might be multiple or recurring initiating events. Different gastrointestinal sites may differ in sensitivity to a possible initiating event (or infectious agent). This could result from a site-specific differential in intestinal permeability or differing immunological responses along the length of the gastrointestinal tract[33,34].

HETEROGENEOUS DISEASE

Crohn's disease remains an intriguing disorder characterized by a granulomatous inflammatory process. The phenotypic clinical expression of Crohn's disease is clearly age-onset-dependent, as most children and adolescents suffer more severe, extensive and complicated disease than most adults and the elderly. If evaluated over a long period of time, the disease appears to be progressive, but only intermittently active, and at a rate that may be very heterogeneous, with some appearing to have prolonged periods of sub-clinical disease and others expressing complex disease with stricture formation and penetrating complications, even at the time of initial clinical presentation. Although the precise cause of Crohn's disease remains a mystery, an increasing appreciation for the long-term natural history of Crohn's disease may permit development of more effective treatment regimens.

REFERENCES

1 **Gasche C**, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ, Sutherland LR. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000; **6**: 8-15

2 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus Jr EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5-36

3 **Freeman HJ**. Application of the Vienna Classification for Crohn's disease to a single clinician database of 877 patients. *Can J Gastroenterol* 2001; **15**: 89-93

4 **Freeman HJ**. Application of the Montreal classification for Crohn's disease to a single clinician database of 1015 patients. *Can J Gastroenterol* 2007; **21**: 363-366

5 **Freeman HJ**. Familial Crohn's disease in single or multiple first-degree relatives. *J Clin Gastroenterol* 2002; **35**: 9-13

6 **Freeman HJ**. Long-term clinical behavior of jejunoileal involvement in Crohn's disease. *Can J Gastroenterol* 2005; **19**: 575-578

7 **Cuthbert AP**, Fisher SA, Mirza MM, King K, Hampe J, Croucher PJ, Mascheretti S, Sanderson J, Forbes A, Mansfield J, Schreiber S, Lewis CM, Mathew CG. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. *Gastroenterology* 2002; **122**: 867-874

8 **Newman B**, Silverberg MS, Gu X, Zhang Q, Lazaro A, Steinhart AH, Greenberg GR, Griffiths AM, McLeod RS, Cohen Z, Fernández-Viña M, Amos CI, Siminovitch K. CARD15 and HLA DRB1 alleles influence susceptibility and disease localization in Crohn's disease. *Am J Gastroenterol* 2004; **99**: 306-315

9 **Abreu MT**, Taylor KD, Lin YC, Hang T, Gaiennie J, Landers CJ, Vasiliauskas EA, Kam LY, Rojany M, Papadakis KA, Rotter JI, Targan SR, Yang H. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology* 2002; **123**: 679-688

10 **Heliö T**, Halme L, Lappalainen M, Fodstad H, Paavola-Sakki P, Turunen U, Färkkilä M, Krusius T, Kontula K. CARD15/NOD2 gene variants are associated with familially occurring and complicated forms of Crohn's disease. *Gut* 2003; **52**: 558-562

11 **Cosnes J**, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250

12 **Louis E**, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; **49**: 777-782

13 **Freeman HJ**. Natural history and clinical behavior of Crohn's disease extending beyond two decades. *J Clin Gastroenterol* 2003; **37**: 216-219

14 **Freeman HJ**. Temporal and geographic evolution of longstanding Crohn's disease over more than 50 years. *Can J Gastroenterol* 2003; **17**: 696-700

15 **Greenstein AJ**, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD, Aufses AH Jr. Perforating and non-perforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. *Gut* 1988; **29**: 588-592

16 **Gryboski JD**, Spiro HM. Prognosis in children with Crohn's disease. *Gastroenterology* 1978; **74**: 807-817

17 **Harper PC**, McAuliffe TL, Beeken WL. Crohn's disease in the elderly. A statistical comparison with younger patients

matched for sex and duration of disease. *Arch Intern Med* 1986; **146**: 753-755
18 **Farmer RG**, Michener WM. Prognosis of Crohn's disease with onset in childhood or adolescence. *Dig Dis Sci* 1979; **24**: 752-757
19 **Polito JM 2nd**, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. *Gastroenterology* 1996; **111**: 580-586
20 **Weinstein TA**, Levine M, Pettei MJ, Gold DM, Kessler BH, Levine JJ. Age and family history at presentation of pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2003; **37**: 609-613
21 **Freeman HJ**. Age-dependent phenotypic clinical expression of Crohn's disease. *J Clin Gastroenterol* 2005; **39**: 774-777
22 **Freeman HJ**. Comparison of longstanding pediatric-onset and adult-onset Crohn's disease. *J Pediatr Gastroenterol Nutr* 2004; **39**: 183-186
23 **Freeman HJ**. Long-term prognosis of early-onset Crohn's disease diagnosed in childhood or adolescence. *Can J Gastroenterol* 2004; **18**: 661-665
24 **Vernier-Massouille G**, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, Merle V, Salomez JL, Branche J, Marti R, Lerebours E, Cortot A, Gower-Rousseau C, Colombel JF. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008; **135**: 1106-1113
25 **Van Limbergen J**, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, Smith L, Gillett PM, McGrogan P, Weaver LT, Bisset WM, Mahdi G, Arnott ID, Satsangi J, Wilson DC. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008; **135**: 1114-1122
26 **Freeman HJ**. Crohn's disease initially diagnosed after age 60 years. *Age Ageing* 2007; **36**: 587-589
27 **Kugathasan S**, Saubermann LJ, Smith L, Kou D, Itoh J, Binion DG, Levine AD, Blumberg RS, Fiocchi C. Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. *Gut* 2007; **56**: 1696-1705
28 **Dubinsky MC**, Kugathasan S, Mei L, Picornell Y, Nebel J, Wrobel I, Quiros A, Silber G, Wahbeh G, Katzir L, Vasiliauskas E, Bahar R, Otley A, Mack D, Evans J, Rosh J, Hemker MO, Leleiko N, Crandall W, Langton C, Landers C, Taylor KD, Targan SR, Rotter JI, Markowitz J, Hyams J. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008; **6**: 1105-1111
29 **Markowitz J**, Kahn E, Daum F. Prognostic significance of epithelioid granulomas found in rectosigmoid biopsies at the initial presentation of pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr* 1989; **9**: 182-186
30 **Gupta N**, Cohen SA, Bostrom AG, Kirschner BS, Baldassano RN, Winter HS, Ferry GD, Smith T, Abramson O, Gold BD, Heyman MB. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterology* 2006; **130**: 1069-1077
31 **Kelly JK**, Sutherland LR. The chronological sequence in the pathology of Crohn's disease. *J Clin Gastroenterol* 1988; **10**: 28-33
32 **Freeman HJ**. Granuloma-positive Crohn's disease. *Can J Gastroenterol* 2007; **21**: 583-587
33 **Meddings JB**, Gibbons I. Discrimination of site-specific alterations in gastrointestinal permeability in the rat. *Gastroenterology* 1998; **114**: 83-92
34 **Camerini V**, Panwala C, Kronenberg M. Regional specialization of the mucosal immune system. Intraepithelial lymphocytes of the large intestine have a different phenotype and function than those of the small intestine. *J Immunol* 1993; **151**: 1765-1776

S- Editor Tian L **L- Editor** Kerr C **E- Editor** Zheng XM