Crohn's disease

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Abstract

Crohn's disease is a chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract from the mouth to the anus, although the ileum, colon and perineum are most commonly involved. It is characterized by transmural granulomatous inflammation. Although the aetiology is unknown, Crohn's disease is thought to result from a complex interplay of multiple genetic and environmental factors. There appears to be an immune dysregulation to microbiota in genetically predisposed individuals. Several genes involved in the interaction between microbiota and the host immune system, in particular the innate immune system, are defective in Crohn's disease, including *NOD2* and the autophagy genes *ATG16L1* and *IRGM*. Diarrhoea, abdominal pain, fatigue, weight loss and fever are the hallmarks of Crohn's disease. The clinical features depend on the location and behaviour of the disease in the gastrointestinal tract. Additionally there are extra-intestinal manifestations affecting joints, skin, eyes and the liver. Investigations are directed towards identifying the location, extent, and severity/behaviour (inflammatory, stricturing, penetrating) of disease. The goal of all therapies should be to achieve clinical and endoscopic remission in time to avoid disease progression and surgical resections. Treatment usually features corticosteroids, immunomodulators (thiopurines, methotrexate), anti-tumour necrosis factor-α (TNFα) therapy or surgery. Patients with poor prognostic features may benefit from early treatment with immunomodulator drugs and/or anti-TNFα therapy. Therapeutic drug monitoring can help physicians to improve and personalize the management of Crohn's disease.

Keywords anti-tumour necrosis factor-α; autophagy genes (*ATG16L1* and *IRGM*); corticosteroids; Crohn's disease; immunomodulators; inflammatory bowel disease; *NOD2*

What's new?

- Incidence of Crohn's disease (CD) is increasing particularly in children and in non-Western societies
- New CD-associated genes have increased understanding of the immunopathogenesis, especially the interplay between microbiota and the innate immune response and autophagy
- Magnetic resonance enterography and endoscopic techniques (wireless capsule endoscopy, double balloon enteroscopy) are useful to assess small bowel involvement
- Patients with poor prognostic features appear to benefit from early treatment with immunomodulator drugs and/or anti-tumour necrosis factor-α (TNFα) therapy
- Laparoscopic surgery is preferable where expertise is available
- Endoscopic mucosal healing is associated with better outcomes
- Drug concentration monitoring to adapt doses of immunomodulators and/or anti-TNFα antibodies can personalize patient management

Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) of unknown cause (idiopathic). It is characterized by transmural granulomatous inflammation and typically involves the terminal ileum, colon and perianal region, although it can affect any part of the gastrointestinal tract from the mouth to the anus, often in discontinuity. Common complications include intestinal strictures, fistulas and abscesses.

Epidemiology

The incidence of CD varies worldwide. Rates vary between 0.1 and 16/100,000 inhabitants, with highest incidence recorded in Northern and Western Europe and North America, while lower rates are recorded in Africa, South America and Asia (Table 1). Overall, CD is less common than ulcerative colitis (UC). The number of people with CD has been steadily increasing, particularly among young people and in non-Western societies. Childhood-onset CD is also becoming more common, especially in those under 10 years of age.[1] Estimates of prevalence vary depending on whether figures are derived from primary (200/100,000 population) or secondary/tertiary care settings (70–100/100,000 population). In a population-based study in Asia–Pacific, the incidence of CD varied across Asia but was still lower than the West.[2] CD can be diagnosed at any age but most commonly presents between 10 and 40 years of age, with a smaller peak in the seventh decade. In Western countries, it is marginally more common in women than in men (the reverse is seen in Asian countries, where there is a male predominance). There is a notably high incidence among Ashkenazi Jews.[3]

Aetiology

Although the cause of CD is unknown, there appears to be a dysregulated host immune response to intestinal microbiota (microbial flora harboured by healthy individuals) in genetically susceptible individuals. Indeed a common theme to emerge from genetic studies of CD is the importance of the innate immune response in handling intestinal microbiota.

Genetic determinants

Fifteen percent of patients with CD have a relative with either CD or UC and the concordance rate in monozygotic twins is about

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Incidence rates of IBD worldwide

	Incidence rate per 100,000	
	Crohn's disease	Ulcerative colitis
Australia	17.2	11.2
North America	20.2	19.2
Europe	12.7	24.3
Asia and Middle East	5.0	6.2

Table 1

45% (higher than for UC). Patterns of disease within families are similar.

There has been significant progress over the last decade in identifying susceptibility genes for CD. Approximately one-third of patients with CD have mutations in *NOD2*, the first CD gene identified, on chromosome 16.[4,5] Compared with the wild type, *NOD2* heterozygotes have a twofold increased risk of developing CD, whereas *NOD2* homozygotes have a 17-fold increased risk. *NOD2* variants are particularly associated with ileal CD. *NOD2* encodes an intracellular receptor for bacterial muramyl dipeptide, and modulates activation of NFκB and downstream pro-inflammatory mediators by a poorly understood mechanism.

Genome-wide association scans in CD have highlighted several other important immune pathways[6]: autophagy, a process involving the degradation of a cell's own components and intracellular bacteria, is highlighted by association of the autophagy genes *ATG16L1* and *IRGM* with CD; and the interleukin-23 (IL-23) pathway is highlighted by association of variants in the IL-23 receptor gene. Overall, there are 163 IBD loci that have been identified and about two-thirds of the genes are shared between CD and UC. There is particular overlap between IBD genes and genes implicated in ankylosing spondylitis and psoriasis.[7]

Genetics can predict disease outcome; for instance, *NOD2* variants are particularly associated with ileal and stenosing CD[8] and earlier need for intestinal surgery. However, despite advances in the field of CD genetics, there are currently no genetic tests that are recommended routinely for disease diagnosis.

Environmental factors

Smoking: smokers are more likely to develop CD than non-smokers (as opposed to UC where smoking is protective) and the disease tends to be more difficult to manage in smokers, who appear to need more immunosuppression and surgical intervention.

Diet: although dietary factors are likely to be of key importance in CD, no dietary components consistently trigger a flare. Excess refined sugar or animal protein and low intake of fibre have been associated with CD, but dietary manipulation of sugars/fibre has had no demonstrable impact on disease presentation or disease course. Breastfeeding appeared to be protective. Elemental or polymeric diets are beneficial treatments for children and adults with CD and are associated with mucosal healing.[9]

Microbiota: evidence implicating microbiota in the aetiology of CD comes from numerous animal models of inflammatory bowel disease, which remain healthy when kept in 'germ-free' conditions but develop colitis when colonized by commensal microbiota.[10] In the closest analogous situation in humans, when the faecal stream of a patient with CD is diverted, the downstream inflammation resolves but reappears when continuity is restored. Many organisms have been suggested, including adherent, invasive *Escherichia coli*, measles virus, *Mycobacterium paratuberculosis*, listeria, *Pseudomonas fluorescens* and *Bacteroides vulgatus*. On the other hand, *Faecalibacterium prausnitzii* appears to be protective.[11] However, as yet, there is no clear evidence for a single organism causing CD; instead, there appears to be an imbalance in the microbiota with altered diversity and richness. The impact of the genetic background, smoking and diet on the microbiota is poorly understood. Recent studies have suggested that antibiotic use during childhood may predispose to disease development.

Immunological factors

Genetic defects in CD have highlighted important immunological pathways, particularly involving the innate immune response, barrier function, defensins, macrophages, antigen-presenting dendritic cells and the Th17 pathway.[12]

Pathology

CD can affect any part of the gastrointestinal tract, in contrast to UC, which affects the colon alone (with occasional backwash ileitis). CD is most often confined to the bowel and can be ileocaecal (40%), exclusively ileal (30%) or exclusively colonic (25%). Perianal involvement occurs in about one-third of patients. Disease tends to be discontinuous, giving rise to 'skip' lesions, and affected bowel is oedematous and associated with fat wrapping on the serosal surface. Mucosal ulceration varies from scattered aphthous ulcers to deep serpiginous pleomorphic ulcers. These can burrow through the bowel wall, leading to fistula formation between the affected bowel and adjacent bowel, bladder, vagina or skin.

Histologically, transmural inflammation predominates although this is usually submucosal. Focal patchy chronic inflammation (lymphocytes and plasma cells), focal crypt irregularity (discontinuous crypt distortion) and non-caseating granulomata (not related to crypt injury) are the generally accepted microscopic features that allow a diagnosis of CD.[13] (Table 2) Granulomata (Figure 1) occur in up to 60% of cases, particularly in distal and perianal disease.

Clinical features

The clinical features depend on the location and behaviour of the disease. CD has been sub-divided using the Montreal classification (Table 3), which takes into account the location of disease in addition to its behaviour (inflammatory; stricturing or penetrating) and the age at diagnosis.[14]

Symptoms and signs

CD may present insidiously or acutely and symptoms can vary from vague gastrointestinal upset to severe systemic features of fever, malaise and tachycardia.

The majority of patients have diarrhoea (70–90%), abdominal pain (45–66%) and/or weight loss (65–70%). Rectal