Arumugam Rajesh
Rakesh Sinha
Editors

Crohn's Disease

Current Concepts

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Dedicated with love to my parents Suresh and Saraswati Sinha
Rakesh Sinha

Dedicated with love to my parents, R. A. Mudaliar and Suseela Arumugam
My wife and daughters Priya, Nethra and Unnathi
And
In memory of my friend Dr. Madhusudanan Sriperumbudur
Arumugam Rajesh

Foreword

The Times They Are A-Changin' – Bob Dylan

Medical historians [1–3] have suggested that the initial description of Crohn's disease may have dated back to Morgagni [4]. Despite new knowledge from immunology, molecular biology, molecular genetics, and other disciplines, this disease ranks as one of the major clinical enigmas of medicine, challenging all scientific disciplines. It is classified medically as an autoimmune disorder, but its causes are not well understood. The disease was named after gastroenterologist Burrill Bernard Crohn, who, in 1932, together with two other colleagues at Mount Sinai Hospital in New York, described a series of patients with an inflammation of the terminal ileum [2–3].

Despite the increasing role of endoscopy and its newer modifications in the diagnosis and management of Crohn's disease, radiology has maintained an important role. Although any part of the gastrointestinal tract can be involved in the disease, the most common site of involvement is the distal small intestine. The complexity in evaluating the intestinal tract, particularly the mesenteric segment, is apparent with the introduction of newer imaging technologies and the refinement of older methods [5–8].

Many people with Crohn's disease have symptoms for years prior to diagnosis. Multiple methods of imaging are used in the initial workup of the patient with suspected Crohn's disease. The subtle difference in the role of radiology in the workup of patients with abdominal pain, diarrhoea, weight loss, or faecal blood, of which small-bowel Crohn's disease is only one of many possibilities, as opposed to the role of radiology in patients with established Crohn's disease, is not well understood by radiologists and referring clinicians. Considerations of local expertise or when to refer a patient for further imaging to a specialist center during initial workup are not emphasized in published guidelines. Guidelines, though not inflexible, have been proposed by several societies and organizations through consensus and the limited available scientific data. An analysis of these guidelines suggests that the efficacy of the imaging methods depended to a large extent on the diagnostic confidence of the referring physician. It is, therefore, not uncommon to see patients undergo several examinations before an appropriate examination is performed and a firm diagnosis established.

The number of well-controlled trials in small-bowel imaging is small and will likely remain this way. Referring clinicians and radiologists must rely on

the "art" of medicine to fill in the deficiency [9–10]. It may not be necessary to establish the true scientific accuracy of an imaging method to understand its efficacy.

Advances in techniques for imaging of the small bowel have been rapid [5, 11–13]. Several imaging methods are at the forefront of this rapidly evolving field of study, which has significant implications in the choice of medical management or the choice between surgical versus nonsurgical management. Newer imaging techniques and the role of older diagnostic methods are in the midst of this "diagnostic revolution."

Medical treatment of Crohn's disease has also undergone rapid advances with the introduction of anti- TNF-α agents. These drugs have improved the quality of life and reduced hospitalizations and number of surgical procedures by inducing and maintaining remission. Surgical advances such as laparoscopic surgery and strictureplasty have also led to reduced hospitalization and morbidity.

This book is a compendium of the current clinical, endoscopic, surgical, radiological, and pathological knowledge and recent advances in Crohn's disease. It is a practical and easy-to-understand reference book for clinicians, surgeons, and radiologists involved in this rapidly changing field. The book also outlines what further advances are needed in this clinically challenging disease entity.

IN, USA Dean D. T. Maglinte, MD

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Preface

Crohn's disease is a chronic relapsing inflammatory disease with both intestinal and extra-intestinal manifestations that predominantly affects young people. Despite new knowledge from immunology, molecular biology, molecular genetics and other disciplines, this disease is one of the major clinical enigmas of medicine challenging several scientific disciplines. It is classified as an autoimmune disorder but its causes are not well understood.
Although excellent textbooks and monographs on Crohn's disease are available, most deal with specific clinical disciplines. Therefore this book has been conceptualized as a practical handbook encapsulating the current medical knowledge on Crohn's disease covering several medical specialties.

The chapters have been written by international experts and describe the current evidence-based information and practical knowledge that is useful in the treatment of Crohn's disease. Special emphasis has been placed on radiology, reflecting the editors' interests, and as it is perhaps the overarching discipline that is intimately involved with the diagnosis, medical and surgical evaluation, follow up and therapeutic interventions in Crohn's disease.

The editors hope this book serves as a compendium of the current clinical, endoscopic, surgical, radiological and pathological knowledge and recent advances in Crohn's disease. It is designed as a practical reference book for physicians, surgeons, paediatricians and radiologists involved in the treatment of Crohn's disease. The book also outlines recent advances and what further advances are needed in this clinically challenging disease entity.

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Aetiology and Clinical Features of Crohn's Disease

1

Simon S.M. Chan and Andrew R. Hart

Contents

Abstract

The aetiology of Crohn's disease is largely unknown, but probably involves a combination of genetic, immunological and environmental factors. This chapter describes the incidence of Crohn's disease and the methodological approaches used to investigate the aetiology. Exposures which could influence the risk of Crohn's disease are discussed, including genetics, smoking, habitual diet, the gut microbiota and commonly prescribed medications, including non-steroidal anti-inflammatory drugs and oral contraceptives. An overview of the clinical features of Crohn's disease is also presented.

Keywords

Crohn's disease • Aetiology • Genetics • Diet • Smoking • Drugs • Microbiota • Clinical features

1.1 Introduction

Crohn's disease (CD) affects approximately two million people worldwide and consists of chronic inflammation affecting any part of the gastrointestinal tract with the terminal ileum and large bowel most commonly affected. The disease has a relapsing and remitting course with most patients requiring medication and surgery. The

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aetiology is largely unknown, but probably involves a combination of genetic, immunological and environmental factors. Identifying exposures which influence the risk is important in efforts to prevent a disease which has a life-long morbidity, impairs patients' quality of life and increases the risk of colorectal cancer. Exposures which can plausibly influence the risk are discussed, including genetics, smoking, habitual diet, the gut microbiota and commonly prescribed medications, including non-steroidal anti-inflammatory drugs and oral contraceptives. Finally, an overview of the clinical features of CD is presented.

1.2 Incidence

The incidence of CD worldwide varies between 0.1 and 16.0/100,000 population/year, with the lowest incidences in Asia and developing countries and the highest in western ones [1]. In high incidence areas, the disease is 20–30 % commoner in females, but in low incidence regions, CD is more prevalent in men [2]. The commonest age at diagnosis is between 15 and 30 years [3, 4], but can occur at any age. In recent decades, the incidence in the West has tended to stabilise, but the illness is becoming more prevalent in Asian countries. The incidence in migrants tends towards that of their adopted country. An increased risk of 50 and 80 % has been documented respectively with increasing latitude in both The United States and across countries in Europe [4, 5]. These descriptive data, which report differences in incidence between populations, and over time, are important to generate hypotheses on the aetiology of CD.

1.3 Methodologies for Investigating the Aetiology of CD

The ultimate aim of etiological studies in CD is to identify differences in risk factors between initially well people who do, and do not, subsequently develop CD. These risk factors include genetic, immunological, environmental and lifestyle ones. Measuring lifestyle exposures such as diet and medication use in etiological studies is complex in that such exposures may be firstly difficult to measure accurately and secondly they may vary over the time prior to diagnosis. Vitally in etiological studies, such exposures need to be documented before the development of symptoms and diagnosis, which then most likely reflect those involved in causation. Recording exposures when a person is unwell leads to error as the disease may alter the level of the exposure itself and therefore be unreflective of that involved in aetiology. For example, if consumption of a particular long-term food causes CD, intake of this food needs to be recorded prior to symptoms, rather than at diagnosis, when less is consumed as the patient is unwell and may be eating less. The ideal and most robust study design investigating lifestyle factors are randomised controlled trials, but in practice for CD these are pragmatically and ethically virtually impossible. Such trials would require recruiting initially well people and then randomising them to a potential harmful exposure to see if they were more likely to develop CD. Similarly, well people could be asked to reduce a particular exposure, such as a food item, but compliance over long time periods could be low. Furthermore, as CD is relatively uncommon, hundreds of thousands, possibly millions of well people would need to be enrolled to accrue sufficient numbers developing the illness. Due to these difficulties, hypotheses on lifestyle exposures must be investigated in observational epidemiological studies namely case-control or cohort investigations. Retrospective case-control studies are pragmatically easier to conduct, although they have inherent recall and selection biases. Recall bias is a particular problem as patients with CD diagnosed months or even years before will have difficulty accurately recalling their pre-symptomatic exposures, such as diet. However, prospective cohort investigations minimise these recall biases as initially well people report their current levels of exposures, a small proportion of whom then subsequently develop IBD during follow-up. Furthermore, cohort studies reduce selection

biases as both subsequent cases, and those who remain well, are drawn from the same baseline population. To date, two such prospective cohort investigations have reported their results on diet, anthropometry and medications: the European Prospective Investigation into Diet and Cancer (The EPIC-IBD study) and the US Nurses' Health Study both of which will be discussed later.

Once risk factors for CD have been identified in epidemiological studies, the next stage is to confirm if they are causal and not purely associations. To assess causality, various criteria need to be met, as described by the English epidemiologist Sir Austin Bradford Hill in 1965 [6]. These propose that for causality, there should be: *plausible biological mechanisms*, *consistent results* from epidemiological studies showing *large effect sizes* in a *dose-response manner* in which the exposure information is *temporal* (measured before symptom onset) and *analogy* (confounding variables) have been considered. Other criteria include *specificity* i.e. a risk factor defines a single disease outcome, *coherence* i.e. a logical connection between the laboratory and epidemiological evidence and *experimental work*, namely interventional clinical trials, although the latter are difficult to conduct in CD.

1.4 Genetics

The genetic susceptibility of inflammatory bowel disease is complex with the aetiology of CD having a greater genetic component than that of ulcerative colitis [7]. Over the last two decades genetic studies have provided many candidate genetic loci that may be involved in the pathogenesis of inflammatory bowel disease. The *NOD2* gene variant is probably the most well-established of these genetic loci identified using a positional cloning strategy [8]. In more recent years, genome-wide association studies (GWASs) have provided a more rapid approach to survey the human genome for genetic loci, including single nucleotide polymorphisms, associated with CD. This is a powerful hypothesis-free methodology that has helped establish the role of the innate and acquired immune systems and their interactions with bacteria in the aetiology of inflammatory bowel disease [9]. Furthermore, GWASs have led to the identification of previously unexpected new mechanisms such as autophagy whose role in CD is becoming more evident. Yet, despite the identification of over 140 genetic risk loci, the risk contribution of these known genetic loci in isolation to CD is estimated to be less than 25 % [10]. Admittedly, a substantial proportion of CD aetiology is not accounted for from existing genetic studies as estimated from twin and epidemiological studies. As missing hereditability alone is unlikely to account for the discrepancy, this implies that other exposures such as environmental factors and the interactions between these and genetics may also be involved.

Environmental variables that may be involved in inflammatory bowel disease aetiology are discussed later, but the concept of epigenetics in CD aetiology is emerging. Essentially, epigenetics can be defined as mitotic heritable changes in gene function not mediated by changes in the DNA sequence. Instead, the main mechanisms of gene expression are altered by DNA methylation, histone acetylation and chromatin package. Importantly, such changes of gene expression can be mediated by environmental factors (e.g. diet, smoking, infections – all of which have been implicated in CD aetiology), and can occur within an individual's lifetime subsequently persisting for multiple generations [11]. One example of epigenetics is a study that examined rectal biopsies, which found that the gene *ULK1* was methylated only in patients with CD [12].

In summary, current evidence suggests that coding variations in IBD genetics only has a modest contribution to disease risk, with the possibility of epigenetic regulation modified by environmental factors playing a much larger role. As neither genetics nor environmental variables in isolation are able to fully account for the risk of developing CD further studies into the interactions of these are required.

1.5 Environmental Factors

Smoking

There are many plausible biological mechanisms for how cigarette smoking could increase the risk of CD, although none have been confirmed. These include: direct toxic effects of chemicals in cigarettes, smoking increasing the viscosity of blood and deleterious effects on the mesenteric vasculature [13]. The epidemiological data reports positive associations, with consistent findings from both case-control and cohort investigations. A meta-analysis of 9 studies of *current versus never smoking* and the development of 10,610 confirmed cases of CD, reported a positive association in a random effects model (OR = 1.76, 95 % CI = 1.40–2.22) [14]. For former smoking, the summary odds ratio was 1.30 (95 % CI = 0.97–1.76, P = 0.08). Although only two of the included studies were prospective cohort investigations, the recall bias for cigarette smoking before symptoms should be low. Similarly, in another meta-analysis of 16 studies comprising 2,962 patients with CD who underwent disease-modifying surgery, smokers had higher clinical post-operative recurrence rates than non-smokers (OR = 2.15, 95 % CI = 1.42–3.27, P < 0.001) [15]. There was evidence of a duration-response effect, with higher re-operation rates in smokers at 10 years rather than 5 years after the initial surgery. A previous meta-analysis from 1989 reported no dose-response relationship in three investigations, although the numbers of subjects was small for sub-group analyses [16]. Therefore smoking is likely to cause CD in view of the consistency of the results from the epidemiological work, including prospective studies, modest effect sizes and some evidence of dose response, in addition to plausible mechanisms for the associations. However, a definite causative link cannot be implied until the pathogenesis of CD is better understood. Such work would also help confirm there are no residual confounders, which explains the association with cigarettes. However, smoking cessation in the general population should be encouraged to potentially reduce the incidence of CD, as well as its other health benefits.

Diet in the Aetiology of CD

Dietary factors are environmental exposures to investigate as foods and nutrients could influence the inflammatory process through several pathogenetic mechanisms. These include: direct toxic effects on the gastrointestinal mucosa, alteration of the gut microbiota and changes in the constituents of the cell membrane itself. To date, nutrients which have been investigated in prospective cohort studies include: polyunsaturated fatty acids (PUFAs), protein, fibre and vitamin D. PUFAs are macronutrients consisting of two main groups, n-3 PUFAs present in fish oils including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which possess anti-inflammatory properties and may therefore lower the risk of CD. N-3 PUFAs inhibit genes activating the inflammatory process, are metabolised to eicosanoids such as prostaglandin E_3 and leukotriene B_5 which have weaker anti-inflammatory properties than those derived from other groups of PUFAs, and are also converted to lipid mediators with both anti-inflammatory and inflammation resolving properties [17–19]. The second group of dietary PUFAs, n-6 PUFAs, include linoleic acid and arachidonic acid, present in red meat, certain cooking oils and margarines. Arachidonic acid, a component of the phospholipid bilayer, is converted to pro-inflammatory eicosanoids, including prostaglandin E_2 and leukotriene $B_{4,}$ which are elevated in the mucosa of patients with CD [20]. Involvement of fatty acids would be supported by prospective cohort studies demonstrating that patients with CD have higher dietary intakes of n-6 PUFAs and lower ones of n-3 PUFAs than well people. To date, there are only two such cohort studies of dietary factors in the aetiology of CD. In the first, The EPIC-IBD Study, 229,702 initially well adult participants completed food frequency questionnaires and were followed up for up to 10 years, during which time 73 developed incident CD [21]. All higher quintiles of DHA intake were inversely associated with the development of CD, although only the highest was statistically significant (OR = 0.07, 95 % CI = 0.02–0.81), with a trend across quintiles (OR trend = 0.54, 95 % CI = 0.30–0.99). No