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Crohn's Disease

Radiological Features and Clinical-Surgical Correlations

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Foreword

Crohn's disease is a chronic pathology that is very difficult to understand and to diagnose especially in the early stages, resulting in a significant deterioration in the patients' quality of life.

In the past, this disease had a higher incidence in the northern Europe countries. Recently we have seen an increase of cases in the Mediterranean area, probably due to environmental factors and changes in lifestyle, becoming increasingly challenging not only for radiologists but also for clinicians.

This book deals thoroughly with Crohn's disease, analyzing the different clinical, diagnostic, and therapeutic aspects. The purpose is to provide a global view of the pathology, necessary to understand the disease in its entirety and in its complexity. In fact these patients cannot be approached in "watertight compartments," but the partnership between the clinician, the radiologist, and the surgeon is more necessary than ever, in order to achieve the most appropriate treatment for each case.

Because of the different presentations, often treacherous and misleading, and the complexity of the several extraintestinal manifestations, only an integrated clinical-radiological approach can lead to proper patient management.

In this scenario, radiological imaging plays an important role, providing various diagnostic options based on the most modern technology. Every diagnostic modality can be exploited differently depending on the various stages of the disease.

The authors involved in this project can boast an internationally recognized expertise, arising from years of research focused on to the study of Crohn's disease. The result of their contribution brings to a complete and integrated text, containing the latest knowledge in this field, providing an extremely useful tool for anyone who decides to tackle this disease.

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Acknowledgments

To my wife Maria Cristina, my daughter Roberta Maria, and to my parents.

Giuseppe Lo Re

To my wife Anna and to my sons Federico and Mauro.

Massimo Midiri

Contents

Epidemiological Aspects of Crohn's Disease

1

Francesco Vitale

1.1 Epidemiology

Crohn's disease (CD) is considered a result of multifactorial interplay between genetic, immune-related, environmental, and infectious triggers all contributing into evolution of clinical disease [1, 2].

The age of onset of Crohn's disease has a bimodal distribution. The first peak occurs between the ages of 15 and 30 years (late adolescence and early adulthood), and the second occurs mainly in women between the ages of 60 and 70 years [3].

In general, the frequency of CD is similar in males and females, with some studies showing a very slight female predominance.

The rate of Crohn's disease is 1.1–1.8 times higher in women than in men. This pattern is reversed with pediatric CD, which has a higher incidence in boys than in girls (pediatric male-to-female ratio, ~1.6:1) [3, 4].

Crohn's disease is reported to be more common in white patients than in black patients and rare in Asian and Hispanic children. Approximately 20 % of all CD patients are of black descent. Rates are higher in people of Jewish descent, particularly in Ashkenazi Jews and Jews of middle European origin as compared with Sephardic or eastern European Jews [4].

Although there are few epidemiologic data from developing countries, the incidence and prevalence of CD are increasing with time and in different regions around the world, indicating its emergence as a global disease [3].

The incidence of Crohn's disease (CD) differs depending on the region studied. Epidemiologic studies conducted during the last decade has mostly supported the idea of a disease of the developed world, with a typical north to south gradient observed in Europe [4].

Overall, the United Kingdom, North America, and the northern part of Europe are the areas with the highest incidence [5].

In North America, the most notable example of long-term surveillance for CD incidence evolution is the Olmsted County, Minnesota, database, encompassing registries from the 1930s onward [6]. A gradual increase has been continuously observed, with the median annual incidence for the 1990–2001 period reaching 7 cases per 100,000 population, compared to 6.6 per 100,000 for the 1965–1975 period. An inversion of the usual female predominance has been observed in recent years, with more male than female patients diagnosed. The typical patients are young and of urban origin.

Studies on pediatric CD in the USA offer less information, describing an annual incidence of 4.5 per 100.000, while the incidence in children

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of Afro-American origin in Georgia was much higher (7.1/10^5/year) [7].

In Canada, the district of Manitoba consistently reports one of the highest incidences of CD worldwide, reaching 14.6/10^5 for the 1987–1994 period: the disease predominates in young females and exhibits a significant variability between smaller geographical regions, and the incidence is characteristically lower in Indian aboriginals, raising the question about a possible different genetic profile. Nevertheless, even in this population, a recent increase has been noted, especially in the 30–40 age group [8, 9].

On the other hand, reports from the 1980s from Quebec and Ontario exhibited significantly low rates: incidence of 0.7/10^5 and prevalence of 33/105 (reflecting a low incidence), respectively [9].

In Central America, the incidence of the disease was recently investigated for the 1996–2000 period, and an increase from 0.49 to 1.96/10^5 was observed in Puerto Rico where CD predominates in young males [10].

The disease seems to be scarce in Latin America: a study from a region of Panama and a region of Argentina showed a practically non-existent disease in the 1987–1993 period, [11] while the cumulative cases reported from Chile in the 1990–2002 period account to a very low incidence also [12].

A Brazilian study from the region of Janeiro also showed low incidence in the 1980–1999 period, although the total new CD cases reported in the 1995–1999 timeframe exhibited an increase of 166 % compared to the 1980–1984 cases [13].

In Europe, epidemiological dynamics of CD can be drawn by the development and continuing evolution of the European Crohn's and Colitis Organization (ECCO) and the European Collaborative study of IBD (EC-IBD) [14].

Overall, incidence data describes a North-South Europe gradient of CD incidence (7 versus 3.9/10^5).

The EC-IBD study showed an high annual incidence rate in adult population in Iceland (8/10^5), in Norway (5.8/10^5), in Sweden (8.9/10^5), and in Denmark (8.6/10^5), whereas reports on the incidence of pediatric CD are contradicting showing a huge increase in CD in children in Stockholm (1.7 to 8.4/10^5 from 1990 to 2001) [15] and a relatively stable annual incidence rates of 2.5/10^5 and 2/10^5 in two studies focusing on pediatric IBD in Norway [16].

In the Baltic former Soviet republics, the only study from this area, Estonia, showed a low incidence (1.4/10^5) compared to Scandinavia [17].

The United Kingdom represents, in Europe, the typical model of North-South gradient, with a potentially higher incidence in Scotland compared to England and Wales. The city of Aberdeen, located in Northern Scotland, demonstrated one of the highest incidences worldwide (11.7/10^5/year) in 1985–1987, with a young urban female predominance. Increasing trends have also been observed in numerous reports on pediatric CD, with the incidence doubling in the 1990s, reaching a median annual rate of 4.4/10^5 in the region of Aberdeen [18].

Other English studies have focused on the racial trends of CD incidence, showing lower prevalence in Southeast Asian residents compared to Europeans or West Indians compared to Caucasians [19].

The incidence rates for Ireland reported in the EC-IBD study are roughly similar to the British ones (6/10^5/year).

Also in Northern France, the EC-IBD study showed high incidence rate of CD (9/10^5/year) [14].

A gradual increase was observed during the 1990s in North France, with the median annual incidence per 100,000 rising from 5.2 to 6.4 from 1988–1990 to 1997–1999, with a female predominance.

A study from the mid-southern French area showed rates comparable to those of Northern France. In the Netherlands, a study from Maastricht had shown annual incidence rates of 6.9/10^5, and in Belgium, a minimal but stable increase was observed through time, with annual rates of 4.5 new cases per 10^5 [20].

In Germany, a study showed a moderate increase in 1991–1995 compared to 1980–1984 (5.2 versus 4.9/10^5/ year), although the median age of the patients increased by almost a decade; the overall German rates reported in the EC-IBD study were slightly lower though [14].

The incidence rates in Southern Europe were invariably low in the EC-IBD study: A North-South gradient was observed in Portugal, where previous studies from Oporto in the north confirmed a steady incidence rise during the 1975–1990 period.

Numerous studies from Spain have failed to reproduce this gradient though: A prospective 1991–1993 study from four regions showed an overall annual incidence of $5.5/10^5$, which was actually higher in the southern region ($6.5/10^5$/year) and the island of Mallorca compared to the northern participating regions [21].

Italy exhibits a typical southern European profile in having low CD rates, but, like Spain, there exists no North-South gradient in the country as such, with a study for eight cities from 1989 to 1992 showing homogenous incidence rates. However, a recent Italian administrative database study on IBD, covering a wide area in central Italy, demonstrated incidence rates during the years 2008–2009 of 7.4 and 6.5 for Crohn's disease for males and females, respectively [22]. The lowest European incidence was reported initially from Northwest Greece, although an increasing trend observed recently and a significantly higher incidence reported from the southern island of Crete [23] (data for both areas until mid-1990s, rates 0.1 and 3/105, respectively).

Traditionally, the incidence has been low in Asia and Africa. However, studies from these areas suggest that the incidence of CD is increasing.

The prevalence of CD in Europe varies from less than 10 to about 150 per 100,000 inhabitants.

An adjusted prevalence of 133 per 100,000 was found in Minnesota, United States, in 1991. One study from South Korea indicated prevalence of 11.2 per 100,000 [24].

Population-based studies have demonstrated that the incidence and prevalence of CD have increased over the last three decades. CD is most common in northern Europe and North America, and there is a slight predominance of women diagnosed with the disease.

1.2 Risk Factors

Genetic, microbial, immunologic, environmental, dietary, vascular, and psychosocial factors, as well as smoking, the use of oral contraceptives and nonsteroidal anti-inflammatory agents (NSAIDs) have been associated with increasing risk to develop Crohn's disease. However, interaction between the predisposing genetic factors, environmental factors, host factors, and triggering event is likely necessary for the disease to develop. Most of the genes thought to be involved in the development of the disease play a role in mucosal immunity, and their products are found on the mucosal barrier epithelium [25].

The first gene clearly identified as a susceptibility gene for Crohn's disease was the NOD2 gene (now called CARD15), in which were identified 3 single nucleotide polymorphisms (SNPs), 2 missense, and 1 frameshift. These variations in NOD2/CARD15, which is a polymorphic gene involved in the innate immune system, play a role in 27 % of patients with Crohn's disease, with CARD15 genotype being associated not only with the onset of disease but also with its natural history. A study in a German and Norwegian cohort showed that patients with 1 of the 3 identified risk alleles for CARD15 were more likely to have either ileal or right-colon disease [26].

An early genome-wide association study (GWAS) looked at Jewish and non-Jewish case-control cohorts and identified 2 SNPs in the IL23R gene, which encodes 1 subunit of the IL-23 receptor protein. Interestingly, this study also described the promising nature of certain therapies that block the function of IL-23. Further research suggested that one particular polymorphism in the IL23R gene showed the strongest association in a German population [27].

In a meta-analysis of 3 GWASs, 526 SNPs from 74 distinct genomic loci were found including the genes CCR6, IL12B, STAT3, JAK2, LRRK2, CDKAL1, and PTPN22 [28]. Most of these genes are involved in signal transduction in certain immune function, as well as genes involved more directly with immune function. Other GWASs found associations between susceptibility to Crohn's disease and polymorphisms, and one large study involving nearly 20,000 SNPs in 735 individuals with Crohn's disease found an association in the ATG16L1gene, which encodes the autophagy-related 16-like protein involved in the autophagosome pathway that processes intracellular bacteria [29]. A large genomic study of multiple diseases confirmed many of the findings found in earlier studies and identified several additional loci of interest for Crohn's disease located within the BSN gene,

which encodes a brain-specific scaffold protein involved in neurotransmitter release and in the NKX2-3 gene, which is a homeodomain-containing transcription factor [30].

Infectious agents such as *Mycobacterium paratuberculosis*, *Pseudomonas* species, and *Listeria* species have all been implicated in the pathogenesis of Crohn's disease, suggesting that the inflammation seen with the disease is the result of a dysfunctional, but appropriate, response to an infectious source [25].

Also interleukins and TNF-α have been suggested to play a role in the disease process, which is characterized by a Th1 cellular immune response pattern that leads to production of IL-12, TNF-α, and interferon gamma with increased concentrations of TNF-α in the stool, blood, and mucosa [31].

Environmental influences such as tobacco use seem to have an effect on Crohn's disease. Smoking has been shown to double the risk of Crohn's disease [32].

It has also been suggested that a diet high in fatty foods may increase the risk of Crohn's disease, whereas concerns about the measles vaccine and the development of the disease have proved to be unfounded [33, 34]. Finally, the relationship between appendectomy and the risk of developing CD has been debated, and in 2009, a systematic review found a relative risk (RR) of 6.69 (95 % CI: 5.42–8.25), for having CD diagnosed following an appendectomy, significantly elevated within the first year after the surgery [35].

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