Med Clin (Barc). 2017;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Review

# Crohn's disease☆

María Pilar Ballester Ferré*, Marta Maia Boscá-Watts, Miguel Mínguez Pérez

*Servicio de Medicina Digestiva, Hospital Clínico Universitario de Valencia, Valencia, Spain*

ARTICLE INFO

*Article history:*
Received 22 September 2017
Accepted 16 October 2017
Available online xxx

*Keywords:*
Diagnostic-therapeutic management
Crohn's disease
Inflammatory bowel disease

ABSTRACT

Crohn's disease is a chronic inflammatory bowel disease of unknown aetiology associated with an impaired immune response, with periods of activity and remission. It is characterized by patchy and transmural lesions which can affect the entire gastrointestinal tract, from the mouth to the anus. The most frequent symptoms are abdominal pain and diarrhoea, which can seriously affect patients' quality of life. The increasing incidence and prevalence of the disease in our area has had a large impact on clinical practice, with the rapid development of diagnostic and therapeutic techniques. To reduce the risk of complications, primary care physicians and gastroenterologists should be familiar with the management of the disease.



## Enfermedad de Crohn

*Palabras clave:*
Manejo diagnóstico-terapéutico
Enfermedad de Crohn
Enfermedad inflamatoria intestinal

RESUMEN

La enfermedad de Crohn es una enfermedad inflamatoria intestinal crónica de etiología desconocida asociada a una respuesta inmunológica alterada que cursa con períodos de actividad y remisión. Puede afectar a cualquier tramo del tracto gastrointestinal, desde la boca hasta el ano, principalmente de forma transmural y parcheada. Los síntomas más frecuentes son el dolor abdominal y la diarrea, pudiendo afectar gravemente la calidad de vida de los pacientes. El aumento de su incidencia y prevalencia en nuestro medio ha condicionado un creciente impacto en la práctica clínica habitual así como un rápido desarrollo de técnicas diagnósticas y terapéuticas. Es por ello que tanto médicos de familia como especialistas deben estar familiarizados con el manejo de la enfermedad.



## Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease of unknown aetiology associated with an altered immune response. It goes through periods of activity and remission, which can seriously condition the quality of life of patients, both physically and mentally as well as in the social and work environment. Therefore, an early diagnosis is essential, followed by an adequate therapeutic strategy in order to avoid the occurrence of complications. Given that it is an increasingly common disease in routine clinical practice, a simple and practical review has been carried out that includes key points for the correct management of the disease.

## Epidemiology

CD affects men and women equally. The age of onset has a bimodal distribution with a first peak between 20 and 40 years and a second between 50 and 60.

Its incidence and prevalence have increased significantly worldwide. It is still greater in developed and urban areas. The countries with the highest annual incidence are Australia (29.3/100,000 inhabitants), Canada (20.2/100,000), New Zealand (16.5/100,000) and Northern Europe (10.6/100,000); while those with the highest prevalence are found in Europe (322/100,000), Canada (319/100,000) and USA (214/100,000).[1]

☆ Please cite this article as: Ballester Ferré MP, Boscá-Watts MM, Mínguez Pérez M. Enfermedad de Crohn. Med Clin (Barc). 2018. https://doi.org/10.1016/j.medcli.2017.10.036

* Corresponding author.
*E-mail address:* mapibafe@gmail.com (M.P. Ballester Ferré).

## Aetiology and pathogenesis

The aetiology of CD is unknown, and its pathogenesis is not completely established. Current evidence suggests that the disease is the result of an alteration in the homeostasis of the bowel mucosa immune system in genetically predisposed individuals under the influence of certain environmental factors.

The following sections show the bases of this theory.

### *Immunity of the intestinal mucosa*

Two factors are mainly involved in the alteration of homeostasis in the bowel mucosa immune system: a defective epithelial barrier function and a defective apoptosis of the T lymphocytes.

Epithelial cells carry out the process of autophagy in which they eliminate the unnecessary cytoplasmic content, thus preventing bacterial dissemination. Defects in the genes related to autophagy (*ATG16L1* and *IRGM*) increase the risk of developing CD.[2]

On the other hand, the NOD-2 receptor is a cytosolic microbial molecular recognition protein that belongs to the family of receptors related to the innate immune response and that is expressed by antigen-presenting cells (macrophages, lymphocytes, Paneth cells and epithelial cells). The NOD-2 variants related to CD contribute to the disruption of intestinal homeostasis by inducing hyperreactivity in certain innate responses and by forcing an excessive response in other pathways.[3,4]

### *Genetics*

There is evidence about the genetic basis of CD. Its prevalence is clearly higher in Caucasians. Ashkenazi Jews have a prevalence 3–4 times higher than that of any other ethnic group,[5] while African-Americans and Asians are those that show lower risk.[6] In addition, individuals from the same family have a higher disease prevalence and aggressiveness, especially monozygotic twins.[7,8]

On the other hand, studies of genome association have found more than 30 specific alleles of CD related to the function of microbial recognition by the innate immune system and autophagy (NOD2, IL23R, HLA-II, STAT3, JAK2, ATG16L1, IRGM, LRRK2, etc.).[9,10]

However, the genetic predisposition is not sufficient for the development of the disease, so its evaluation is not recommended in usual clinical practice.

### *Environmental factors*

Smoking is the most-related factor to CD since it increases up to 2 times the risk of suffering from the disease.[11] A history of appendectomy, exposure to antibiotics in childhood, oral contraceptives, aspirin or nonsteroidal anti-inflammatory drugs also seem to increase the risk of CD,[12–14] while statins decrease it.[15] Factors such as breastfeeding or contact with animals in childhood have proven to be protective.[5] However, there is no causal relationship between any of the environmental factors and the development of the CD.

### *Microbiota*

More and more studies show the implication of microbiota in the pathogenesis of the disease. An example is the increased presence of antibodies against microbial components (anti-*Saccharomyces cerevisiae* antibodies, antibodies against porin C of the outer membrane of the *Escherichia coli*, anti-flagellin or anti-glucan antibodies).

On the other hand, patients with CD show a decrease in bacteroid and firmicutes groups (*Faecalibacterium prausnitzii*, commensal bacteria with anti-inflammatory properties) and a greater number of bacteria associated with the mucosa (adherent and invasive *E. coli*).[16,17]

## Clinic and diagnosis

The form of presentation of CD is very heterogeneous and varies depending on the site, extension, degree of activity and disease pattern. The most frequent symptoms are abdominal pain and chronic diarrhoea. Abdominal pain is usually located at the right iliac fossa and may be intermittent or constant. In ileal involvement, diarrhoea is usually of large volume and without pathological products, while in colonic involvement the volume is smaller but includes blood and mucus (more like ulcerative colitis). At the time of diagnosis, systemic symptoms such as malaise, fever, asthenia or anorexia and weight loss are also common. In children, delayed growth or pubertal maturation is typical. Approximately 30% of patients start with perianal disease and up to 50% have extraintestinal manifestations at the time of diagnosis, mainly articular, cutaneous or ocular.[18,19]

Once the clinical suspicion is established, the diagnosis is based on the combination of clinical, biochemical, endoscopic, histological and/or radiological criteria (Table 1).[20]

### *History-taking and physical examination*

In history-taking, besides checking and evaluating the characteristics of the 2 most frequent symptoms, abdominal pain and diarrhoea, it is necessary to investigate the risk factors related to CD, smoking or family history, as well as the taking of drugs, the consumption of alcohol or recreational drugs, travel to parasite endemic areas or the intake of products in poor condition.[7,8,21,22] It is important to know the existence of previous extraintestinal diseases that can guide the diagnosis, mainly joint manifestations or perianal lesions. We must also consider other diseases that occur with diarrhoea such as food intolerances, bacterial overgrowth, celiac disease or hyperthyroidism.

The signs of systemic toxicity such as fever, tachycardia or hypotension, as well as the state of hydration and nutrition should be evaluated. The abdominal examination may show a painful hardening at the level of the right iliac fossa. Perineal, anal and rectal examination should evaluate the presence of both external lesions (cutaneous tags, fistulous orifices, bulges) and in the anal canal (fissures and ulcers, stenosis or secretions).[18]

### *Lab tests*

It is important to evaluate the nutritional parameters since it is not uncommon in CD to find hypoalbuminemia and vitamin deficiencies (mainly vitamin $B_{12}$), especially in patients with ileal involvement. It is also common to find anaemia and iron deficiency.[23] Hepatic biochemistry should be performed (among others to rule out the association of primary sclerosing cholangitis). Elevation of acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate or thrombocytosis is typical. However, no parameter correlates adequately with the degree of inflammatory activity and up to a third of patients present normal figures in the presence of activity. Other markers increasingly used in clinical practice are lactoferrin and, especially, faecal calprotectin. The latter is a protein present in the cytoplasm of neutrophils, useful both for the screening of patients with suspected CD and to monitor the degree of activity and response to treatment as it shows a good correlation with endoscopic and even histological inflammation.[24] However, it is not specific enough to the CD, so its value will be higher with a normal result to rule out inflammation. In case of high levels, a possible enteric infection should be considered by performing stool cultures, including *Clostridium difficile*.[25]