

Crohn's Disease: Pathophysiology, and Management

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ABSTRACT

Background: The incidence of crohn's disease reaches up to 20 per 100,000 people per year, with a median age of 30 years, and is higher in the developed world. Although the exact cause and pathophysiology is unknown, several environmental and genetic factors have been linked with higher risk or severity of the disease.

Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: crohn's disease, inflammatory bowel disease, genetics of crohn's disease, diagnosis of IBD, management crohn's disease

Aim of the study: In this review, we aim to study the pathophysiology, diagnosis and management of crohn's disease. We will pay special attention to the newer biological drugs used in management.

Conclusion: Crohn's disease is usually managed with medical treatment, although many patients will need to undergo surgery at least once. Treatment usually aims at the induction and maintenance of a remission without the excessive use and dependence of steroids. Achieving higher quality of life is the main goal of any modality of treatment.

Keywords: Crohn's disease, inflammatory bowel disease, medical management for crohn's disease.

INTRODUCTION

In 1932, **Dr. Burril Crohn** and his team described 'crohn disease' for the first time. Crohn disease is considered an inflammatory bowel disease 'IBD' with idiopathic etiology and chronic nature. Recent reports have found IBDs to attack more than 1 percent of the general US population.

The incidence of crohn disease can reach 20 per 100,000 person-year, with a median age of 30 years. It has a bimodal distribution with a pick at twenties and another around fifties. The prevalence and incidence of crohn disease is higher in the developed world (like North America and Western Europe) than developing world (like South America and Asia) ^[1]. It is slightly higher among women and tends to have higher incidence among Ashkenazi Jewish. Until now, it is still not known how crohn's disease develops and what causes the observed pathological findings. However, several environmental and genetic factors have been linked with higher risk or severity of the disease ^[2].

METHODOLOGY

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1988, through February 2017. The

following search terms were used: crohn's disease, inflammatory bowel disease, genetics of crohn's disease, diagnosis of IBD, management crohn's disease.

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout. **The study was done after approval of ethical board of Taif university.**

Etiology

The exact etiology is still unknown, and the most famous hypothesis suggests that crohn disease is an autoimmune disease that attacks individuals with genetic susceptibility.

The onset of the disease was found to be influenced by environmental exposures that affect the natural balance of the gut flora, alter the mucosal protection, and stimulate abnormal immune responses in the GI tract. Gut flora (microbiota), gut immune response, and genetic predisposition, all work together with the environmental factors to develop crohn's disease ^[3].

Genetics

Crohn disease and ulcerative colitis share many of the genetic predisposition with about 110 loci shared between them. Additionally, crohn disease has 30 loci specific for it. Natural killers (NK), NKT cells, CD4 T, and dendritic cells (DCs) were all found to be associated with the pathophysiology of crohn disease ^[4].

Disease Phenotype

Crohn disease is subdivided into three phenotypic types: fistulizing, stricturing, and inflammatory. In inflammatory crohn disease, there is GIT inflammation without the presence of fistulas or strictures. Inflammatory crohn disease will consequently cause narrowing of the lumen with fibrosis, and the disease will then be classified as stricturing. This fibrotic changes are considered irreversible and the only possible treatment is surgery. The conversion of the disease into a fistulizing crohn disease requires continuous transmural inflammation that will lead to the formation of a fistula or a sinus tract. Fistulae can form between any organs near the guts. Examples include the urinary bladder, vagina, and other near organs. An intra-abdominal abscess may also occur if the sinus fails to complete between the gut and the organ. Perianal complications and manifestation may also occur in any of the previous subtypes, and are not considered a separate subtype, but a long-term sequelae. The Montreal classification is the standardized most updated classification used to diagnose and treat crohn disease. Age, site, and behavior are all considered in this classification ^[5-7].

Signs and Symptoms

Any part of the gastrointestinal tract can be affected in crohn disease, with about half the patients have terminal ileum involvement. About one third of the patients have involvement of the small intestines only, and only one fifth of the patients have isolated damage of the large intestine. Perianal sequelae are estimated to develop in about one quarter of patients. These complications include fissures and fistulae. Isolated perianal complications, extraintestinal sequelae, or upper GI involvement occur only in less than ten percent of crohn disease cases ^[8].

Presentation varies between patients and is directly associated with the site and the phenotype of the disease. In some cases, patients may suffer from

many symptoms for long years before establishing a diagnosis. Classical presentations include diarrhea, and abdominal pain along with systemic manifestations like fever, weight loss, and fatigue. Stricturing crohn disease will additionally cause obstruction of the gastrointestinal tract (most likely the small intestines). Obstruction of the intestines presents with decreased movements and flatus, increased bowel sounds, vomiting, and/or nausea ^[8]. In cases of a penetrating crohn disease, fistulae and abscesses are formed.

An abscess will additionally cause fever, chills, and other constitutional symptoms. Acute peritonitis can rarely be the presenting symptom of penetrating crohn disease. Other symptoms that can happen in a penetrating crohn disease include diarrhea when there is an enteroenteric fistula, the presence and passage of stool from vagina when there is an enterovaginal fistula, skin drainage when there is an enterocutaneous fistula, and UTIs when there is enterourethral or enterovesicular fistula. Severe crohn disease can cause the presence of blood in stool, although this is usually associated with ulcerative colitis ^[9; 10]. Management plan should not be solely based on signs and symptoms, and endoscopy, imaging, and markers should also be taken into consideration (which will be discussed later in this review).

Diagnosis

Clinical diagnosis of crohn disease is usually challenging due to the insidious nonspecific nature of the disease. Weight loss, iron deficiency anemia, bloody diarrhea, night-time awakenings, elevated C-RP and ESR without a clear cause, a family history of an inflammatory bowel disease, or decreased vitamin B12 levels are all considered red flag symptoms that necessitate further investigations for a possible diagnosis of crohn's disease ^[8].

Confirmation of the disease will require pathology. In cases of an ileal or colonic crohn's disease, endoscope will typically reveal skip lesions with inflammation (varying in degree) characterized by the presence of erosions, ulcers, friability, and erythema, along with areas of normal mucosa. Additionally, strictures and fistulae can also be seen during endoscopy. Although present in less than one quarter of cases, non-caseating granuloma is a classic finding under the microscope. On the other hand, the presence of infiltrates of lymphocytes, granulocytes, crypt architecture disruption, crypt

atrophy, plasma cells, basal lymphoplasmacytosis, crypt abscesses or branching, and shortening of the crypts are all considered classical common pathological findings in crohn disease. Paneth cell metaplasia is also present and indicates the chronicity of the disease. In rare cases where the jejunum is solely affected, endoscope may not clearly show the pathology, and a balloon or capsule endoscopy should be performed to provide proper assessment of the small intestines [11; 12].

Imaging modalities can also be used during the assessment of crohn disease. CTE and MRE usually provide a clear bowel and mucosa visualization with the ability to detect extra-luminal complications if present. MRE is considered more expensive than CT, but has the advantage of preventing exposure to radiation [13].

Serologic markers have also been used in the assessment and diagnosis of crohn disease. However, until now there is no marker that is specific or sensitive enough to confirm or deny a diagnosis of Crohn's disease [14].

Management

Crohn disease treatment is largely dependent on the site of the disease, its severity, and its phenotypical subtype. Medical therapy aims at maintaining a remission status and avoid the need for surgery. Surgery is the only treatment when there is formation of structuring or fistula. Unfortunately, patients with crohn disease are likely to need several surgeries as surgery does not provide a complete cure of the disease [15].

Drugs

Medical management of crohn disease include several agents. Several studies on mesalamine have not found it to be effective in induction or maintenance of remission. However, it is related to a relatively safe profile, making it a widely-used drug in crohn disease. The use of antibiotics has also been increasing in crohn disease although to evidence is present to support their use. Antibiotics are mainly used to prevent or treat perianal or suppurative sequelae of crohn's disease. Mercaptopurine (MP), azathioprine (AZA), Methotrexate (MTX), and other immunosuppressants, are characterized by a slow action onset, and are usually used in the maintenance of crohn disease remission. The use of AZA/MP along with anti-TNF drugs have been found to provide a good overall efficacy with AZA and MP

playing a role in providing higher anti-TNF concentrations. In fact, anti-TNF drugs have been the most important drugs for treatment of crohn's disease [16; 17].

Monoclonal antibodies against IL-12, IL-23, integrin $\alpha 4$, or integrin $\alpha 4\beta 6$, were also approved in the treatment of crohn disease. Natalizumab is the first approved monoclonal antibody against integrin, but it has been associated with the development of a fatal brain condition: progressive multifocal leukoencephalopathy (PML). Another anti-integrin monoclonal antibody that is selective for the guts is vedolizumab.

The use of vedolizumab has not been found to be associated with the development of PML, and therefore is used in the maintenance of remission status even in severe crohn disease cases. However, it is not sufficiently effective in inducing remission. Ustekinumab is a monoclonal antibody against IL-12 and IL-23 that was recently approved and shown to provide effective induction and maintenance of remission even in severe crohn disease. In conclusion, medical therapy mainly targets the induction and maintenance of remission without the use of steroids, the prevention of complications requiring surgery, and -most importantly- improvement of the quality of life [18; 19].

Surgery

Almost all patients with crohn disease will require surgical intervention at some time during their disease progression. Situations that require surgery include stricturing, fistulas, perianal manifestations, infections or obstruction. Other cases where surgery is indicated are dysplasia, cancer, or failure of medical therapy. Determination of the exact surgical intervention will be according to the indication of the surgery [20].

CONCLUSION

Crohn disease is an inflammatory bowel disease that affects any part of the GI tract. It is usually managed with medical treatment, although many patients will need to undergo surgery at least once. Treatment usually aims at the induction and maintenance of a remission without the excessive use and dependence of steroids. Achieving higher quality of life is the main goal of any modality of treatment. Awareness of histological and clinical subtypes are essential to provide a proper

management plan and predict prognosis and possible complications.

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