Crohn's Disease

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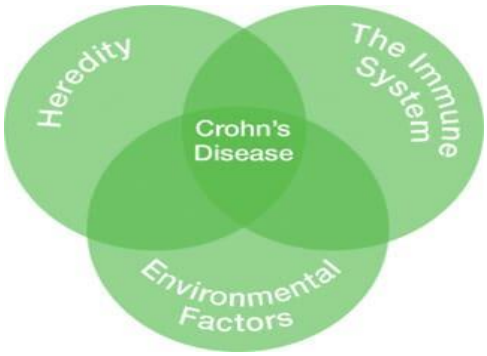
Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease, with a complex aetiology involving genetic, environmental, and immunological factors. It is characterised by recurring episodes of inflammation, ulcerations, and strictures, leading to a wide range of symptoms and complications. [1]



https://www.crohnsandcolitis.com/crohns/causes

Over 40,000 people in Ireland are living with inflammatory bowel disease (IBD). Of these approximately 20,000 people are affected by colitis and Crohn's Disease.[6] Crohn's disease can affect people of any age but usually starts between the ages of 15 and 35, while a second smaller peak can occur from the ages of 50s to 70s. CD affects men and women equally, with a slight female predominance in adult onset Crohn's disease. Incidence and prevalence are higher in high income countries and in urban areas, with a high incidence in Northern Europeans and among the Ashkenazi Jewish population.[1, 4] IBD is complex and costly, and its increasing prevalence places a greater stress on health care systems. [9]

Crohn's disease can affect any part of the gastrointestinal tract. 50% of patients have terminal ileum and colon involvement, while 30% have small-bowel only involvement, and 20% of cases are isolated to the colon. In addition, 25% of patients experience perianal complications including fissures and fistula. Less frequently (<10%), patients present with isolated perianal complaints, upper gastrointestinal disease, or extra intestinal manifestations (EIMs) which can affect the skin, joints, eyes, liver, blood vessels, and kidneys. Arthritis is the most common EIM affecting up to 25% of patients with CD. There is no cure and most patients experience bouts of remissions and relapse at unpredictable times. [1]

In Crohn's disease, the inflammation extends through the entire thickness of the bowel wall from the mucosa to the serosa. The disease runs a relapsing and remitting course. With multiple relapses, it can progress from an initially mild or moderate inflammatory condition to a severe penetrating and stricturing disease. CD has a significant impact on the quality of life of affected individuals, necessitating early diagnosis and appropriate management strategies.[1]

Pathophysiology

The pathophysiology of Crohn's disease is multifactorial in nature, involving genetic predisposition, infectious, immunological, environmental, and dietary factors. A major role is played by alterations at the level of immunity and inflammation. Innate immunity is involved in terms of defects in the mucous barrier (MUT2 and FUT2 genes) while adaptive immunity relies on a T_H1 lymphocytic response and T_{REG} cells mediated by cytokines like TNF-α, IL-12, IL-34 and IL-23. The increased migration to the sites of inflammation is also determined by a reshaping of the extracellular matrix through the action of metalloproteins MMP-1 and MMP-3 and the overexpression of adhesions molecules such as MAcCAM-1 and integrin α4β4. [2]

The characteristic transmural inflammation can include the entire GI tract from mouth to the perianal area; although it most frequently involves the terminal ileum and right colon. The initial lesion starts out as an infiltrate around an intestinal crypt. This leads on to ulceration first in the superficial mucosa and then the deeper layers. As the inflammation progresses, non-caseating granulomas form involving all layers of the intestinal wall. It can develop into the classic cobblestone mucosal appearances and skip lesions along the length of the intestine sparing areas with normal mucosa. As the flare of Crohn settles, scarring replaces the inflamed areas of the intestines. Granuloma formation is very common in Crohn's disease but absence does not exclude the diagnosis. Ongoing inflammation and scarring can lead to bowel obstruction and stricture formation. Crohn's disease is also associated with enterovesical, enteroenteral, enterocutaneous, and enterovaginal fistulas. [3,4]

Pathophysiology [4]

Not fully understood

- **Immunobiology: impaired intestinal barrier function and dysregulation of the innate and adaptative immune system responses, with an alteration of gut microbiota**
  - **Deficient mucus biofilm barrier: decreased expression of mucin secretion genes (*MUC1, MUC19* and *PTGER4*) in the terminal ileum in patients with Crohn's disease**
  - **Permeability changes in the intestinal epithelium: altered expression of tight junction proteins (claudin)**
  - **Paneth cell dysfunction**
  - **Impaired autophagy of invasive microbes**
  - **Imbalance of effector T cells and naturally regulatory T cells**
  - **Recruitment and erratic retention of leukocytes**
- **Dysbiosis:**
  - **Continuous alterations in intestinal microbiota resulting in clustering and reduced diversity in Firmicutes and Bacteroidetes phyla**
  - **Reduction in *Faecalibacterium prausnnitzii* was associated with an increased recurrence of ileal Crohn's disease in the postoperative setting**
- **Genetic risk factors:**
  - **Increased risk for individuals who have family history**
  - **Concordance in monozygotic twins is 20 - 50% compared with 10% in dizygotic twins**
  - **Wide genome association studies identified 200 loci associated to Crohn's disease; however, they contribute only a modest relative risk increase**
  - ***NOD2, ATG16L1, IL23R* gene variants are responsible for some of the heritable risk**
- **Environmental risk factors:**
  - **Cigarette smoking doubles the risk of developing Crohn's disease**
  - **Reduced fibre dietary intake**
  - **Antibiotic therapy during childhood increases the risk of developing Crohn's disease**
  - **Other medications including nonsteroidal anti-inflammatory drugs, oral contraceptives and aspirin**

Breastfeeding appears to be a protective factor against the development of Crohn's disease

Risk Factors

Environmental factors can include smoking, antibiotics, nonsteroidal anti-inflammatory drugs and reduced fibre diet. While the role these factors play is not fully known, they can act as triggers to initiate a harmful immune response in the GI tract.[8] Smoking is the most notable risk factor for developing Crohn's disease, aside from family history and ethnic background. Smokers are twice as likely to develop Crohn's compared to non-smokers, and those who smoke usually experience more severe symptoms compared to those with the condition who do not smoke. While there is no evidence that diet plays a role in Crohn's disease, certain types of food and drink have been associated with worsening symptoms including milk, dairy products, alcohol, processed, spicy and fatty foods. There is no diet or eating plan that will work for everyone with Crohn's disease and dietary recommendations must be tailored individually. Some research suggests that a Mediterranean style diet is associated with an improved quality of life and reduced disease activity in Crohn's disease. Some probiotics have also demonstrated small benefits. Although flares are often associated with stressful events, there is no evidence to prove that stress causes or contributes to Crohn's disease. [1, 6,7]

Presenting symptoms

There are 3 main phenotypes of CD: inflammatory, stricturing, and penetrating. Presenting symptoms are variable and some patients may have symptoms for years before a diagnosis of Crohn's disease is made. Patients with inflammatory disease often present with abdominal pain and diarrhoea, and may develop more systemic symptoms including weight loss, low-grade fevers, and fatigue. Patients with stricturing disease may develop bowel obstructions while those with penetrating CD can develop fistula or abscesses. When an abscess is present, in addition to abdominal pain, patients can have systemic symptoms such as fever and chills and may also present with signs of acute peritonitis. [5]

Diagnosis

The diagnosis of Crohn's disease can be quite challenging given that presenting symptoms can be insidious and nonspecific. A detailed patient medical history and physical examination is carried out. Blood tests can highlight the presence of anaemia (B12 or iron deficiency) or liver disease. Special serology such as normal anti-neutrophil cytoplasmic antibodies (ANCA) and raised anti-saccharomyces cerevisiae antibodies (ASCA) can distinguish Crohn's disease from ulcerative colitis. C-reactive protein (CRP) or erythrocyte sedimentary rate (ESR) can reflect the severity of the inflammation. Stool tests to rule out infections include culture and sensitivities, ovum and parasites, clostridium difficile toxins, and leukocyte count. Stools for calprotectin can detect active Crohn's disease and are also used for monitoring the illness. Plain x-rays are ordered if bowel obstruction is suspected. The perineum should be examined in all patients, and may reveal skin tags, ulcers, fistulas, scarring, and abscess. Frank perforation is rare but can be a presentation of Crohn's disease.[1]

Symptoms that require further investigation include weight loss, bloody diarrhoea, iron deficiency, and night-time awakenings. A significant family history of IBD, unexplained elevations in the C-reactive protein level, sedimentation rates, or other acute phase reactants such as ferritin and platelets, or low B12 should prompt further investigation. [1]

There is no single test that can be used to confirm or disprove a diagnosis of Crohn's disease. The diagnosis is made based on symptoms, endoscopic and radiologic findings. (Colonoscopy, Biopsy, SBE, CT, MRI, Wireless Capsule Endoscopy). Pathology can also be confirmatory. [1,5,7] Endoscopy with histological evaluation remains the gold standard for diagnosing CD. However, advanced imaging techniques, such as magnetic resonance enterography (MRE) and computed tomography enterography (CTE), have emerged as valuable tools for evaluating disease extent and complications. Biomarkers, such as faecal calprotectin and C-reactive protein, aid in disease monitoring and predicting disease activity.[1,5]

Complications

Crohn's disease is associated with extraintestinal manifestations including episcleritis, uveitis, stomatitis, aphthous ulcers, liver steatosis, gallstones, cholangitis, primary sclerosing cholangitis, nephrolithiasis, hydronephrosis, urinary tract infections, arthritis (sacral spine, knee, ankles, hips, wrist, elbows), ankylosing spondylitis, erythema nodosum, and pyoderma gangrenosum. Thromboembolic disease can be a complication of Crohn disease, and may present with deep vein thrombosis, stroke, or pulmonary embolism. Patients with Crohn's disease have an increased risk for colorectal cancer.[1,4]

Differential

Other conditions can mimic the symptoms of CD and it is important to rule out infection and other causes even when patients with known CD are having flare-ups. Patients with diarrhoea should be assessed for infection, IBD, and in certain cases coeliac disease. Other conditions that may present like CD include appendicitis, Behcet disease, and Ulcerative Colitis. **[1]** It is important not to confuse inflammatory bowel disease (IBD) like Crohn's disease or ulcerative colitis with irritable bowel syndrome (IBS). IBS is a disorder that affects the muscle contractions of the bowel and is not characterised by intestinal inflammation, nor is it a chronic disease. **[8]** Both Crohn's Disease and Ulcerative Colitis (UC) are inflammatory bowel diseases (IBDs), but there are some key differences. [8]

Crohn's Disease	**Ulcerative Colitis**
Inflammation may develop anywhere in the GI tract from the mouth to the anus	Limited to the large intestine (colon and rectum)
Most commonly occurs at the end of the small intestine	Occurs in the rectum and colon, involving a part or the entire colon
May appear in patches	Appears in a continuous pattern
May extend through entire thickness of bowel wall	Inflammation occurs in innermost lining of the intestine
About 67% of people in remission will have at least 1 relapse over the next 5 years	About 30% of people in remission will experience a relapse in the next year

Treatment and Management

The diagnosis, treatment and management of Crohn's disease requires a multi-professional team approach. Patient education regarding their illness is very important. There are several medications available to treat Crohn's disease**,** however, there is no cure. The mainstay of treatment is medical therapy with the goal of achieving clinical, endoscopic and histologic remission, demonstrated by mucosal healing. Treatment is chosen based on the disease stage, severity and location. Dietician input and nutritional supplementation are highly recommended before and during the treatment of Crohn disease.[1, 4]

Steroids

Steroids are used to induce remission but are not an effective maintenance agent. Steroids are usually only used to treat the active disease because their long-term use is associated with a range of adverse side effects. Budesonide and prednisolone are two steroids that are often used to treat Crohn's disease. [1,5,7]

Budesonide is usually the first choice of steroid prescribed to help control the symptoms of Crohn's disease. Taken on a short-term basis of less than 12 weeks budesonide may cause acne, oedema of the face, hands, arms, feet and legs, mood changes, insomnia and indigestion. If taken for more than 12 weeks, budesonide may cause osteoporosis, increased vulnerability to infection, cataracts, muscle cramps and stiffness, and vitamin D and calcium supplements will be required to help protect against the effects of osteoporosis. Due to increased vulnerability to infections, close contact with people who are known to have infections, particularly those with chickenpox, measles and shingles should be avoided. [1, 5,7]

Prednisolone is used in cases where budesonide proves ineffective. It has the same type of short and long-term side effects as budesonide, and has also been known to cause mental health problems in an estimated 5% of people.[1, 5]

Aminosalicylates

Sulfasalazine belongs to a group of medicines called aminosalicylates, known to reduce inflammation inside the colon. Sulfasalazine can be used as an alternative to steroids to treat mild cases of Crohn's disease. Common side effects include headache, nausea, abdominal pain and diarrhoea. [1,5]

Immunosuppressants

Immunosuppressants are used in maintenance therapy and in combination with steroids when a person has a relapse of symptoms. Immunosuppressants used for treating Crohn's disease include methotrexate, azathioprine, tacrolimus and mercaptopurine. Side effects of azathioprine include increased vulnerability to infection, bleeding and bruising. Less common side effects include headaches, shortness of breath, dizziness, nausea and vomiting. [1,5, 12]

Mercaptopurine originally developed to treat leukaemia has since proved effective in the treatment of Crohn's disease. Given in tablet form, its side effects are not as severe as those associated with other forms of chemotherapy treatment. Common side effects include nausea and vomiting while less common side effects include loss of appetite, fatigue, breathlessness and weakness caused by anaemia. Effective contraception if sexually active is important while taking mercaptopurine, as it temporarily affects both ova and sperm and can increase the risk of birth defects. [1, 5]

Biological Therapies

Biological therapies are a new type of medication created using naturally occurring biological substances, such as antibodies and enzymes. Two main biological therapies are infliximab and adalimumab. Infliximab is usually only recommended in severe cases of Crohn's disease that have not responded to steroid and immunosuppressant treatments, and where the person is unsuitable for surgery. [1,12]

Infliximab works by targeting the tumour necrosis factor (TNF) antibodies that are responsible for much of the inflammation associated with Crohn's disease. Given by intravenous infusion, around one in four people has an allergic reaction to infliximab and experiences symptoms such as joint and muscle pain, itchy skin, high temperature, rash, swelling of the hands and/or lips, problems swallowing and headaches. Symptoms range from mild to severe and usually develop in the first two hours after the infusion has finished. [1, 5,11]

Adalimumab works in a similar way to infliximab by targeting TNF antibodies. It is given by injection and most people will need to have an injection every two weeks. Like infliximab, adalimumab increases vulnerability to infection, and those taking it should avoid contact with people with chickenpox or shingles and always report any symptoms of a possible infection to their GP. Adalimumab can cause reactivation of the hepatitis B virus and may not be suitable for people who were previously infected. Common side effects of adalimumab include pain, swelling, redness and itching at the site of the injection, headache, and abdominal pain, nausea, vomiting, skin rash, muscle, joint and bone pain and respiratory tract infections, such as colds and pneumonia. [1,5,11]

The goal of medication management is to control the inflammation and induce a clinical remission with pharmacological therapy, however, most patients will eventually require surgery. Surgery is not curative, and patients still require ongoing therapy even after surgery for disease recurrence. [1, 6]

Surgery

Surgery is required when the symptoms of Crohn's disease cannot be controlled using medication alone, and for complications such as bowel obstructions, abscess, fistulas, or perforated bowel. During surgery, the inflamed section of the digestive system is removed and the remaining part is reattached. An estimated 80% of people with Crohn's disease requires surgery at some point in their life. Surgery does not cure Crohn's disease, but it can

provide long periods of remission, often lasting several years. A stoma may be required if the disease or inflammation is so severe that an immediate anastomosis is not safe. In some instances, the stoma may be temporary and can be closed once the severe inflammation and infection is controlled. A colostomy is also required if the rectum is removed. [1,5,6, 10]

Despite optimal therapy, most patients with Crohn's disease have a poor quality of life, and life expectancy is slightly reduced due to the risk of development of malignancies, genitourinary disease, liver, and biliary tract complications. A holistic person-centred approach is required in the management of patients with Crohn's disease, who face a lifelong challenging condition that can be emotionally and physically debilitating. The role of the Healthcare Professional is to provide ongoing assessment, management, support and education. Key roles involve establishing a therapeutic relationship with the patient, assessing their understanding of the condition, establishing goals and expectations for successful management of their condition and evaluating their physical, emotional, and psychological well-being. Common concerns for patients are adherence to their therapeutic regimen, pain and discomfort. Many patients experience anxiety, anger, frustration, stress and depression, and their psychological needs should be adequately addressed. Assessment, monitoring, audit and evaluation for disease activity, progression, and the effects of the therapeutic regime on a patient with Crohn's disease is a continuous process. By implementing person-centered care, monitoring and evaluating symptoms, outcomes and responses to therapy, HCPs play a pivotal role in managing the illness and improving the patient's quality of life.

Complementary and alternative medicine (CAM)

Some people report complementary and alternative medicines (CAM) (including fish oils and probiotics) helpful in controlling certain symptoms of Crohn's disease, however, there is little scientific data to support their effectiveness. Although many types of CAM are generally safe, issues of purity, contamination with toxic metals, lacing with prescription drugs, and the side effects of some traditional herbal remedies must be considered. Large well-designed RCTs are needed to validate specific CAM therapies, before they can be incorporated into evidence based medical treatments. [13]

Support groups

Crohn's and Colitis Ireland (CCI) is a support organisation in Ireland for people who are living with, or impacted by, Crohn's disease or ulcerative colitis. They support people who are living with IBD, along with their parents, partners, family and friends. CCI work to improve the quality of life and well-being of the IBD community through sensitive support services, including advocacy, provision of information, training and events, and encourage and educate healthcare professionals in the importance and value of peer support as an adjunct to their management of IBD. For more information visit: https://crohnscolitis.ie/ [6]

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