CROHN’S DISEASE

Objectives

When the student has completed this module, he/she will be able to:

1. Identify the three causes of Crohn’s disease.
2. Identify the basic pathological process of Crohn’s disease.
3. Identify three common complications of Crohn’s disease.
4. Identify a lifestyle factor that causes/exacerbates Crohn’s disease.
5. Identify three common complications of Crohn’s disease.
6. Identify three body systems that may be affected by Crohn’s disease.
7. Identify three classes of drugs that are used to treat Crohn’s disease.
8. Identify a rationale for using surgery as a treatment for Crohn’s disease.

Introduction

Crohn’s disease is a chronic, idiopathic, inflammatory disease of the digestive tract. It is relatively common: there are approximately 7 cases per 100,000 population, and the incidence appears to be increasing.\(^1\) The exact etiology of Crohn’s is not known, but it is currently believed that bacterial and environmental factors, operating in a genetically susceptible host, are the causative factors.\(^2\) There is, at this point, no cure for Crohn’s disease, but advances in surgery and the use of anti-inflammatory drugs and immunosuppressive drugs have done much to reduce the morbidity and mortality of Crohn’s disease.\(^3\)

Epidemiology

Crohn’s disease affects females to a slightly greater degree: one author reports the male:female ratio to be 1.1:1.81.\(^4\) It is more commonly found in Caucasians than in Asians, Hispanics, or African-Americans.\(^5\) Most cases occur before the age of 30 – the peak age of onset is between 15 and 30 years – but there is another peak between 60 and 80 years.\(^5\) However, the disease may be diagnosed at any age.\(^6\) The disease is more common among people of Jewish ancestry. People in urban areas are affected more, as are those in higher socioeconomic classes.\(^6\) It is more common in societies where dairy products and/or carbohydrates make up a large part of the diet.

Etiology

Genetics

There is an undoubtedly a genetic contribution to the development of Crohn’s disease. There is a high concordance rate among twins and a 10-25 fold increased risk of developing the disease in relatives of people with Crohn’s.\(^8\) Again however, although
there is clear evidence of a genetic predisposition to the disease (e.g., mutations in a gene called nucleotide-binding oligomerization doma-2), the exact contribution of family history to the development of Crohn’s disease is not known.

Environmental

Most authorities agree that environmental factors are probably contribute to the development of Crohn’s disease, but aside from cigarette smoking (cigarette smokers are twice as likely to develop Crohn’s disease), it has been difficult to determine what these factors are, how they help cause Crohn’s disease, and their contribution to its pathogenesis.9 It interesting that the incidence of Crohn’s disease is increasing, and especially so in areas that are rapidly becoming industrialized: this provides support for the idea that Crohn’s is, at least partially, caused by environmental influences.10 Other environmental factors that may play a part in developing Crohn’s disease are a history of appendectomy (the inflammation of the appendix may predispose the gut to Crohn’s), the use of oral contraceptives (the oral contraceptives can cause thrombi and the gut may develop small infarcts), a high intake of sugar, a high intake of monounsaturated and polyunsaturated fats, a previous infection with measles infection, and a mycobacterial infection.11

Immunological

The systemic immune problems seen with Crohn’s disease, the nature of the lesions of Crohn’s disease, and the success of immunosuppressive drugs in treating this condition clearly indicate that the immune system is involved in its development.12 Also, there is some evidence that the activity of certain immune cells, e.g. CD4+ cells, is changed in patients with Crohn’s disease, and that the disease is caused by an inappropriate immune response to normal gut flora – the autoimmune theory. However, it is also possible that the immune response seen in Crohn’s disease is a result of a response to an infectious agent.13 It may be that the original problem is a deficient immune response that allows for bacterial/environmental factors to initiate the inflammatory response that causes the signs and symptoms of Crohn’s disease.14

Etiology: Summary

Genetic, environmental, and immunological factors all appear to be involved in causing Crohn’s disease. Certain genetic mutations make the bowel more susceptible to damage caused by environmental factors (e.g., cigarette smoking, bacterial infection) and/or the normal gut flora, and there is altered immune response that causes the inflammation so typical of Crohn’s.

Clinical Presentation

The inflammation of Crohn’s disease starts focally then enters into the deeper layers of the gut and causes granulomas (usually). Subsequently, ulcers and fissures form. The
inflammatory process involves the entire thickness of the wall of the bowel and can cause fibrosis, obstructions, and strictures.\textsuperscript{15}

One third of all cases of Crohn’s disease affect the small bowel exclusively, and most commonly in those cases, the disease affects the terminal ileum. The disease can also affect the small bowel and the colon together, the anorectal area alone, and the colon area alone. One third of patients have perianal involvement (fissures, abscesses, fistulas). A few patients develop ulcers in the mouth and upper intestinal tract.\textsuperscript{16}

Clinically, Crohn’s patients present with a variety of signs and symptoms.\textsuperscript{17,18}

- Prolonged diarrhea
- Abdominal pain and cramping: these are often caused by meals, are due to partial obstruction of the bowel, and relieved by defecation
- Weight loss
- Lack of energy
- Blood or pus in the stool (with colonic involvement)
- Fever
- Anemia: Poor absorption of vitamin B\textsubscript{12} and/or folate
- Palpable, tender mass in the lower abdomen

**Learning Break:** The signs and symptoms of Crohn’s disease are non-specific and can be caused by other medical conditions. The diagnosis is confirmed with an endoscopic evaluation. There are characteristic patterns of inflammation and damage to the intestinal mucosa that are seen and these, along with the presence of strictures, help distinguish Crohn’s from ulcerative colitis.

**Laboratory Findings/Diagnostic Studies**

Laboratory findings are non-specific, although anemia and hypoalbuminemia (due to a variety of causes, e.g., poor protein absorption) elevation of C-reactive protein, and leukocytosis are common.

Imaging studies – barium studies, CT scan – will show thickened loops of bowel, strictures, ulcerations, and abscesses. Capsule endoscopy may also be used as a diagnostic tool. In this procedure, a capsule with a camera and a light source is introduced into the gut and direct visualization is possible.

**Complications**

There are many relatively common complications associated with Crohn’s disease.\textsuperscript{19,20}

**Abscesses**

- Malnutrition: Poor absorption of nutrients and discomfort associated with eating can lead to malnutrition and weight loss. Mineral and vitamin deficiencies are common, but it is rare for a patient to have clinical evidence of these deficiencies.
- Obstruction: The longer the course of the disease, the greater the risk of developing an obstruction.
• Fistulas: The longer the course of the disease, the greater the risk of developing a fistula.
• Perianal disease.
• Cancer: Patients with Crohn’s disease are at an increased risk of developing colon cancer, lymphoma, and small bowel adenocarcinoma, although the latter two are rarely seen. The risk factor is uncertain – there are several estimates that are cited in the literature – but although no one knows the exact risk for intestinal cancer in patients with Crohn’s disease, the risk is real and it increases the longer the patient has the disease and the younger the age at which it was diagnosed. The prognosis for these patients varies; for patients with small bowel adenocarcinoma, it is particularly poor.

**Learning Break:** Although the risk of cancer is not extremely high for patients with Crohn’s disease, they do have a greater chance of developing a carcinoma than the general population and they should have screening colonoscopies performed earlier in life than is usually recommended.

• Crohn’s disease of the esophagus: This is a rare form of the disease, occurring in about 0.3 to 2% of all adults with Crohn’s disease. In almost all cases, other parts of the gastrointestinal tract are affected: there have been only a few cases of Crohn’s limited to the esophagus. It is particularly difficult to treat and the long-term complications of strictures can be very debilitating.
• Hemorrhage: This is possible, but it is uncommon.

There are also a variety of systemic complications that can occur.\(^{21,22,23}\)

• Ocular: Blurred vision, tearing, burning, decreased visual acuity, and photophobia may be seen. These occur in approximately 10% of all patients diagnosed with Crohn’s. Uveitis is possible and if untreated may cause blindness.
• Musculoskeletal: Approximately 22% of all patients with Crohn’s will have musculoskeletal problems. Ankylosing spondylitis, osteoporosis, ostopenia, and fractures are possible.
• Dermatologic: The incidence of cutaneous complications is approximately 2% to 34%, and erythema nodosum (raised, red, tender subcutaneous nodules) and pyoderma gangrenosum lesions (erythematous papules or pustules) can be seen in approximately 20% of all patients with Crohn’s disease. Psoriasis is also common.
• Pulmonary: Bronchiectasis, broncholitis, and asthma are possible complications of Crohn’s.
• Hepatic: Approximately 5% to 15% of all patients with Crohn’s disease develop liver problems. Hepatic complications can include elevation of liver enzymes, pericholangitis, sclerosing cholangitis, autoimmune active hepatitis, and cirrhosis.
• Psychological: The incidence of depression in patients with inflammatory bowel disease has been reported to be triple that of the normal population.\textsuperscript{24}

**Learning Break:** The younger you are when Crohn’s is diagnosed, the greater the risk is of developing a severe case of the disease and suffering complications.

**Learning Break:** There are suspicions that many of the complications of Crohn’s disease are autoimmune in nature and caused by genetic susceptibility, immunopathogenic autoantibodies against antigens in the affected organs, or cytokine imbalances or other mechanisms.

**Treatment**

Crohn’s disease manifests with periodic flare-ups and periods of remission. The basic goal of therapy is to treat the flare-ups and maintain remission. However, standard measures have not been shown to be effective for interrupting this natural course of the disease, and clinicians are beginning to use some of the traditional treatment options earlier and more aggressively – and there evidence in the pediatric literature that suggests this approach can be successful.

**Dietary Treatment**

Malnutrition can be a significant problem for patients with Crohn’s disease – the severity of malnutrition is often directly proportional to the severity of the individual case – and diet can be an integral part of treating it. For many years, patients with Crohn’s disease were treated, in part by “resting” the bowel. It was thought at the time that antigens in food and from bacteria in the gut stimulated an inflammatory response and keeping the gut empty decreased the presence/activity of these antigens. This has subsequently been shown to be unnecessary. Depending on the site of involvement and the presence/absence of strictures, patients should be on either a high-fiber or low-fiber diet. Lactose intolerance is common and the diet should be adjusted to avoid uncomfortable symptoms. Some authors have noted that enteral nutrition has been tried as a technique for maintaining periods of remission, but it has not proved to be successful.\textsuperscript{25} However, this issue is still unresolved and there is recent information that suggests that enteral nutrition can induce remission, and do it quite successfully. Unfortunately, even in cases in which enteral nutrition has been successful, the compliance rates are low; the taste and monotony of the diet can be very discouraging. Total parenteral nutrition can be used, but it is no more successful than other diet therapies. Several small studies have found that enteric-coated omega-3 fatty acid supplements can help maintain remission, but more work needs to be done before these products can be considered to be mainstream therapy.
Surgical Treatment

Surgery is a common therapeutic intervention for Crohn’s disease: up to 70-90% of patients with Crohn’s will require surgery at some point. Surgery is performed when the patient has not responded to medical therapy, or the patient has complications, e.g., stricture, abscess, perforation, or fistulas, or the patient cannot comply with medical therapy. Surgical resection is the most common operation and can be performed for obstruction or a fistula; this can be done using the open technique or laparoscopically: the laparoscopic technique takes longer to perform, but it is less expensive, there are fewer complications, and the hospital stay is shorter.

The rates for recurrence are relatively high, and this is probably because removing the entire affected bowel is difficult and Crohn’s disease often affects large segments of the gastrointestinal tract. Approximately 24%-35% of all patients will require another operation five years after the first, and approximately 40%-70% will require surgery 15 years after the initial operation.

Leaning Break: Cutaneous, ocular and joint disorders are relatively common complications of Crohn’s disease, and surgery tends to decrease their severity. Unfortunately, surgery does not decrease the severity of the other complications, e.g., hepatic, vascular, etc.

Pharmacological Treatment

There are many drugs that can be used to treat Crohn’s disease.

- Antibiotics: These can be used to treat sepsis, but they have no use in managing active disease.
- 5-Aminosalicylate drugs: The 5-ASA drugs are derivatives of salicylic acid and include sulfasalazine and mesalamine. They work by virtue of their anti-inflammatory properties. Sulfasalazine is useful for treating an affected colon (the drug is released in the large bowel) while mesalamine is more useful for small bowel disease. These drugs have been used for many years to treat Crohn’s disease, but there is some doubt about their true effectiveness.
- Corticosteroids: These are the drugs of choice for treating an acute attack of Crohn’s disease. They are not used as maintenance drugs because of the potential for serious side effects and lack of efficacy. Examples of the corticosteroids that can be used to treat Crohn’s are prednisone, methylprednisolone, and hydrocortisone. Budesonide is also used; it is effective and causes fewer side effects and complications than the other drugs.
- Immunomodulators: Thiopurines (e.g., azathioprine, mercaptopurine) can be administered as adjuncts to other therapies when treating active disease. They are often used for patients who cannot tolerate corticosteroids, and they have been shown to induce and maintain remission. Methotrexate can also be used.
- Smoking cessation: Smoking increases the risk of developing Crohn’s and smokers also typically have a more aggressive form of the disease. Smoking
interferes with the effectiveness of some therapies, and smokers have are much more likely to have relapses.

- Biological drugs: Anti-tumor necrosis factor drugs are another treatment option. Tumor necrosis factor is a cytokine. Cytokines are proteins and glycoproteins that are involved in the immune response and inflammatory activity of Crohn’s disease. Anti-tumor necrosis drugs (infliximab, adalimumab, and certolizumab) which inhibit the anti-inflammatory actions of anti-tumor necrosis factor have been shown to be effective in treating relapses, treating patients that are unresponsive to other therapies, and as maintenance drugs. Other biological drugs – monoclonal antibodies, recombinant human interleukin, anti-interferon antibodies – have also been used with varying measures of success.

- Probiotics: Probiotics have been studied as agents that can induce and maintain remission in patients with Crohn’s disease. Probiotics are dietary supplements, live bacteria or yeasts, that are thought to help maintain healthy flora of the gut and in the case of people with Crohn’s, they are thought to improve the immune system of the gastrointestinal tract. Although there is a lot of information about probiotics in the medical literature, the evidence is inconclusive. Some of the data suggest that probiotics may confer a small benefit and it does not appear that they interfere with conventional therapy, but at this point, it is not clear what place probiotics have in treating Crohn’s disease.

**Psychological Issues**

Crohn’s disease can be debilitating and incapacitating and even when the disease is in remission, patients are psychologically affected by it. There has long been a suspicion that people with Crohn’s disease who are susceptible to stress or who are depressed suffer more symptoms and that these factors influence the course of the disease. There is no definitive evidence to support this idea but regardless, it is clear that many people with Crohn’s will need, at times, significant psychological support to cope with their situation. The exacerbations and remissions can be unpredictable, surgery can be very stressful, energy levels can be very low, and drastic changes in lifestyle may be necessary.

But although the need for psychological/emotional support for patients with Crohn’s disease is very real, no one knows what type of therapy is most effective and who will benefit from it, and a review of the studies that explored the use of psychotherapy for Crohn’s disease patients found that it can help – obviously – people who are depressed or anxious, but it is unlikely that it can affect the physical course of the disease. However, the authors of this study did state that for some people, psychotherapy can be very helpful.

**References**