A REVIEW OF CROHN'S DISEASE

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ABSTRACT

Crohn's disease is a chronic relapsing inflammatory bowel disease that may affect any part of the gastrointestinal tract. The ileum, colon, and perineum are most commonly affected. It is characterised by transmural inflammation, and granulomata may be present. Whilst the aetiology of Crohn's disease is not completely understood, it is thought to be caused by the complex interplay between genetic, immunological, microbiological, and environmental factors. Current opinion is that, in genetically susceptible individuals, there is an immune dysregulation to an environmental factor, and the intestinal microbiota plays a central role. Genetic studies of patients with Crohn's disease have found several gene mutations which affect the innate immune system. Two important mutations contributing towards the pathogenesis of Crohn's disease are Nucleotide-binding oligomerisation domain-containing protein 2 (NOD2) and autophagy-related 16-like 1 (ATG16L1). The most common symptoms of Crohn's disease are diarrhoea, abdominal pain, weight loss, and fatigue. Symptoms reflect the site and behaviour of disease, and the presence or absence of strictures and fistulae. Extraintestinal manifestations may be present and typically affect the eyes, skin, joints, or biliary tree. Investigations are performed to map the disease location, assess disease severity, and survey for complications of the disease or treatment. Management is with smoking cessation, steroids, immunomodulators, anti-tumour necrosis factor (TNF) therapy, or surgery.

Keywords: Anti-tumour necrosis factor alpha (anti-TNFα), autophagy genes, Crohn's disease, immunomodulators, inflammatory bowel disease, metabolomics, metagenomics, NOD2.

INTRODUCTION

Crohn's disease is a chronic idiopathic condition characterised by relapsing inflammation of the bowel. Any level of the gastrointestinal tract may be affected from the mouth to the anus, with the ileum, colon and perineum most frequently involved. Extraintestinal manifestations (EIMs) may occur and can affect the skin, joints, liver/biliary tree, and eyes.

Crohn's disease can cause significant morbidity with symptoms including abdominal pain, diarrhoea, faecal incontinence, rectal bleeding, weight loss, and fatigue. The prevalence is increasing in both the West and in the developing world. Crohn's disease particularly affects young adults at a time in life when they are in education, starting work or family lives, and it can have a major impact on quality of life.

EPIDEMIOLOGY

Crohn's disease is more common in the West than developing countries. Northern Europe and the USA have the highest rates of Crohn's disease.[1] In the West, there is also a north/south divide, with rates in Northern Europe of 7 per 100,000 person-years, compared with 3.9 in Southern Europe; with a similar pattern seen in Northern latitude USA compared with Southern latitude USA (hazard ratio 0.48 in the South).[2] Rates in the West have generally been increasing, but are now thought be to plateauing.[1]

Ethnicity also has an effect on presentation of Crohn's disease; in the USA, African Americans are more likely to have colonic and perianal disease and less likely to have ileal disease than their white counterparts. African Americans are also more likely to require hospitalisation as a result

of their Crohn's disease.[3,4] Rates in the East are increasing, especially in China and India.[5] Migrants from developing nations to the West develop rates above that of their birth country.[6] Jews, in particular Ashkenazi Jews, have a high prevalence.[7] There is a bimodal distribution of age at presentation, with the main peak at 10-40 years of age, with a smaller peak in the 60s.

AETIOLOGY

The aetiology of Crohn's disease is incompletely understood. It is known that immunological, microbiological, lifestyle, and genetic factors are implicated. Current opinion is that in genetically susceptible individuals, there is an immune dysregulation to an environmental factor, and the intestinal microbiota plays a central role.

GENETICS

Family history is a major risk factor for Crohn's disease. Having a first degree relative with the disease increases the risk 10-fold; and 9-15% of patients with Crohn's disease have an affected first degree relative. The highest risk is with monozygotic twins, where disease concordance is between 35-50%.[8] There has been major progress over the last decade in identifying susceptibility genes for Crohn's disease through Genome-wide Association studies (GWAS) and now over 160 independent susceptibility loci have been found. The first Crohn's disease gene identified was Nucleotide-binding oligomerisation domain-containing protein 2 (NOD2). NOD2 homozygotes have a 17-fold increased risk of developing Crohn's disease, whilst heterozygotes have a 2-fold increased risk. Interestingly, patients with Crohn's disease who originate from China and Japan do not have the NOD2 mutation.[9] Impaired autophagy[10] (self-digestion by a cell through the action of enzymes originating within the same cell) is increasingly implicated in the pathogenesis of Crohn's disease, and mutations at both NOD2 and autophagy-related 16-like 1 (ATG16L1) loci are associated with disrupted autophagy.

IMMUNOLOGY

Mutations at gene loci coding for immune molecules and pathways, identified via GWAS, have implicated a range of immunological 'culprits' involved in the pathogenesis of Crohn's. Defects in both the innate and adaptive immune systems are present in Crohn's disease. Barrier function, the first line of innate defence, is impaired by both an inadequate mucous layer, and by abnormally low levels of protective antimicrobial peptides (such as the human α-defensin produced in health by Paneth cells), which admit greater antigenic and microbial exposure to the epithelium. Dendritic cells, with their ability to control tolerogenicity are the key link between the innate and adaptive immune systems. Dendritic cell distribution, expression of toll-like receptors, co-stimulatory markers and homing markers, as well as secretion of cytokines, are all altered in Crohn's disease.[11,12] The role of the adaptive immune system in Crohn's disease is characterised by an imbalance between pro-inflammatory effector cells such as Th1 and Th17 (secreting pro-inflammatory mediators including IL12, IL17 and Tumour necrosis factor alpha [TNFα]) and regulatory cells including Tr1 and Th3 (secreting regulatory cytokines such as IL10 and transforming growth factor-beta [TGFβ]).

ENVIRONMENTAL FACTORS

Smoking

Smoking is an independent risk factor for developing Crohn's disease, and has been widely studied. For patients with Crohn's disease, smoking increases progression to more advanced disease (stricturing and/or penetrating); and cessation of smoking is associated with a reduction in progression to advanced disease, and a reduced need for surgery.[13,14]

Diet

Since diet provides the bulk of the antigenic stream that passes through the intestine it would seem likely that dietary factors are relevant in the aetiology of Crohn's disease. However, no food component has yet been proven to be clearly implicated in the pathogenesis. Elemental and polymeric diets, both with lower antigenic load than a normal diet, are successful treatments for Crohn's disease in children. A recent large population-based study has shown that high intake of long chain 3-PUFA (n3-polyunsaturated fatty acid) may be protective against ulcerative colitis (UC), whilst high intake of transunsaturated fats may predispose to disease. The data were not significant for Crohn's disease.[15]

Microbiome

The microbiome consists of billions of microorganisms that line the intestinal mucosa. The composition of the flora within the microbiome is affected by host and environmental factors (diet, antibiotics, etc.). The converse is true also, with the microbiome able to alter mucosal cell DNA sequences. The sheer size of the microbiome, together with its important symbiosis with intestinal immunity, has led to some observers calling the microbiome an organ in its own right. Modern techniques, especially high resolution mass spectroscopy and nuclear magnetic resonance, have enabled detailed study of the constituents of the microbiome. Developments in the field of metabolomics[16] may allow detection of specific microorganism products, through the recognition of unique chemical signatures in waste products such as urine or faeces.

Metagenomic sequencing (analysis of the DNA content of an entire environmental system – in this case the microbiome) is another evolving area of research that is adding to our understanding of the composition of the microbiome.[17] From these studies it is known that the ratio of numbers of bacteria of the four main phyla differ when comparing active Crohn's disease with healthy controls. Reduced firmicute (especially *Faecalibacterium prausnitzii*) and *bacteroides spp*. organism ratios are associated with disease. The use of metagenomic and metabolomic techniques to compare gut microbiota composition in health and in disease has unearthed potential pathogenic pathways, and it is hoped that novel biomarkers of disease will be revealed. Clinically, the importance of the microbiome for driving inflammation is demonstrated by the healing of downstream mucosa after diversion surgery in Crohn's disease, and the recurrence of inflammation after continuity is restored.

PATHOPHYSIOLOGY

Crohn's disease is characterised by transmural inflammation of any part of the gastrointestinal (GI) tract. The most common disease locations are the distal ileum, the colon, and the perineum, indeed it is unusual to have isolated disease elsewhere in the absence of involvement of at least one of these sites. Multiple sites may be diseased, and the pattern of healthy mucosa between diseased segments is termed 'skip lesions' and is typical of Crohn's disease. The deep inflammation allows penetrating (fistulising) and stricturing disease. Histologically the disease is recognised by transmural inflammation, with lymphocyte and plasma cell infiltration, crypt disruption and the presence of non-caseating granulomas.

CLINICAL PRESENTATION

The symptoms are largely dictated by disease location and the presence or absence of strictures and fistulae. Since there are multiple possible disease sites, the presenting feature may be very varied. The most common presenting symptoms are diarrhoea, weight loss, abdominal pain, and fatigue. The Montreal system (Table 1) is used to classify the disease, and the features included are important in determining prognosis and optimal therapy.

EIMs predominantly affect the skin (erythema nodosum, pyoderma gangrenosum), the joints (small joint polyarthropathy, large joint arthropathy, ankylosing spondylitis), the eyes (episcleritis, scleritis and uveitis), and the biliary tree (primary sclerosing cholangitis [PSC]). Patients with Crohn's disease also have an increased risk of venous thromboembolic disease, colorectal cancer (CRC),[18] gallstones, renal stones, and osteoporosis. Recently, an increased risk of malignant melanoma[19] (MM) has been identified, independent of immune suppressant medication

Table 1. Montreal classification of Crohn's disease.

Age at diagnosis	Location	Behaviour
A1: <16 years	L1: Ileal	B1: Inflammatory
A2: 17-40 years	L2: Colonic	B2: Stricturing
A3: >40 years	L3: Ileocolonic	B3: Penetrating
	L4: Upper GI disease	P: Perianal disease

(azathioprine is known to increase the risk of non-MM skin cancers). Optimal skin protection in the sun is imperative.

The increased risk of CRC secondary to chronic colonic inflammation has necessitated implementation of colonoscopic surveillance. The interval between surveillance endoscopies is dictated by the presence or absence of other risk factors and is usually every 1, 3 or 5 years. Other pertinent risks factors include disease severity, disease extent, family history of CRC, presence of post-inflammatory polyps, PSC, dysplasia, and previous colonic stricture.

DIAGNOSIS

Crohn's disease is a clinical diagnosis that relies on history and examination, in combination with laboratory, radiological, and histological investigations. The history must include: type, onset, duration, and severity of symptoms; as well as past-medical, drug, and family histories. The physical examination should include BMI, abdominal examination (especially for tenderness and right iliac fossae masses), perineal and rectal examinations, as well as assessment for EIMs. It is important to consider differential diagnoses; especially mycobacterial disease, where the standard immunosuppressive therapy for Crohn's disease might cause a significant progression of tuberculosis infection.

Laboratory Tests

Full blood count, renal function, liver function, albumin, and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) are all mandatory tests. Anaemia and thrombocytosis are common findings. Anaemia may be due to deficiencies of iron, folate or vitamin B12. Stool tests should include microscopy and culture; *Clostridium difficile* toxin assay and faecal granulocyte proteins (calprotectin or lactoferrin). Infection is a readily treatable precipitant of exacerbations of Crohn's disease, and therefore it is important to screen for infection with every flare. Faecal granulocyte proteins were initially used to distinguish IBS from organic bowel pathologies. More recently, their ability to predict disease relapse has led to their use in clinical decision-making about escalation and withdrawal of treatment, and about the need for endoscopy. For example, when assessing disease activity in a patient on anti-TNF, a high faecal calprotectin value is predictive of disease relapse and might dissuade the clinician from withdrawing the anti-TNF.[20]

Endoscopy

Ileocolonoscopy with biopsies is the gold standard investigation for diagnosing Crohn's disease, for assessment of disease activity and for surveillance for dysplasia and cancer. Typical endoscopic features include isolated aphthous ulcers, cobblestoning, and deep ulceration. The presence of deep ulceration indicates severe disease whilst post-inflammatory polyps (pseudo-polyps) suggest previous severe inflammation. Gastroscopy is recommended in children, or adults with upper gastrointestinal symptoms. Capsule endoscopy is well validated for small bowel Crohn's disease, and is used when other modalities have not provided a diagnosis.[21,22] It is sensitive,[23] but not specific,[24] and cannot provide a tissue diagnosis. Double balloon enteroscopy is sensitive for small bowel lesions,[25] and can obtain histological samples, but is expensive, time-consuming, frequently requires general anaesthesia, and is not available in all centres.

Imaging

Fluoroscopy (barium and Gastrografin® follow-through), which has long been the mainstay of abdominal imaging in Crohn's disease, has been superceded by CT and MR enterography (CTE and MRE), but still provides good images in skilled hands. CTE and MRE have similar diagnostic yield to one other.[26,27] The major advantage of MRE is the lack of ionising radiation which is important in a cohort of patients likely to need repeated imaging. Both modalities, CTE and MRE, may detect mucosal inflammation, strictures, dilated bowel, fistulae, and abscesses. A recent study showed MRE to be as good as CTE in detecting abdominal fistulae.[27] MR is superior for pelvic investigation, and does not involve ionising radiation (a significant consideration in a cohort of patients who require numerous cross-sectional scans), although lower radiation CT techniques are being introduced. Any combination of two of these three modalities offers the highest sensitivity.[28] Ultrasonography has the advantage of avoiding ionising radiation,[26] but is highly operator dependent.

Standard abdominal radiography is useful for emergency presentations as a quick, cheap, and easy test to assess small bowel dilatation and colonic inflammation.

VALIDATED DISEASE SEVERITY ASSESSMENT TOOLS

In clinical practice, probably the most frequently used assessment tool is the Harvey-Bradshaw Index (HBI) (Figure 1). Its popularity is linked to its simplicity, as it is comprised entirely of clinical parameters. Although somewhat subjective, it is used to assess disease activity and to aid treatment decision.

MANAGEMENT

Therapeutic goals include: induction and maintenance of clinical and endoscopic remission, swift resolution of exacerbations, maintenance of adequate nutrition, regular surveillance for complications, monitoring for and avoidance of adverse drug-induced effects, and optimising quality of life. A distinction must be made between inducing and maintaining remission. Steroids, for example, are effective at inducing remission, but lack of long-term efficacy alongside potent adverse effects render them unsuitable for maintenance therapy. Patient education is increasingly recognised to improve compliance with therapy. The type of therapy depends upon disease location and severity, the presence of complications, and lifestyle factors; as a result, treatment pathways must be individualised.

Some patients have a relatively benign disease course without developing significant complications, whilst others suffer chronic poor health and frequent complications. Risk stratification is vital to ensure that those with a benign disease course are not subject to the risks of over-treatment, and conversely to avoid unnecessary disease progression and complications through under-treating those with aggressive disease. Table 2 lists clinical, endoscopic and laboratory predictors of aggressive disease which, if present, should cause consideration of a more aggressive ('top-down') therapeutic approach at an early stage.[29]

Questions:

1. General wellbeing (0=very well, 1=slightly below average, 2=poor, 3=very poor, 4=terrible)
2. Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)
3. Number of liquid stools per day
4. Abdominal mass (0=none, 1=dubious, 2=definite, 3=tender)
5. Complications (1 point each)
   - Arthralgia
   - Uveitis
   - Erythema Nodosum
   - Aphthous Ulcers
   - Pyoderma Gangrenosum
   - Anal Fissure
   - New Fistula
   - Abscess

Results:

- <5 Remission
- 5-7 Mild Disease
- 8-16 Moderate Disease
- >16 Severe Disease

Figure 1. Harvey-Bradshaw Index.
A points-based scoring system used to aid with the assessment of severity of Crohn's disease.

Table 2. Clinical, endoscopic, and laboratory predictors of aggressive disease.

Predictor
Rectal/perianal disease
Extensive small bowel disease
Deep endoscopic ulceration
Young age
Active smoker
Steroids required at diagnosis
Serological markers – ASCA, OmpC, anti-I2, CBir1s[30]
Genetic – NOD2

Smoking

Cessation of smoking is an effective intervention in the treatment of Crohn's disease. Smoking predisposes to a more aggressive disease course, with stricturing and fistulising disease.[14,31]

Diet

Polymeric and elemental diets are effective at inducing remission in children, but less so in adults.[32] This may relate to compliance. A low residue diet helps prevent sub-acute bowel obstruction in patients with stricturing disease. Although diet may not treat Crohn's disease, nutritional assessment and supplementation are important.

Aminosalicylates

Published meta-analyses are inconsistent with regards to efficacy of 5-ASA in Crohn's disease. European guidelines are that 5-ASAs are not recommended for maintenance of medically-induced remission of Crohn's disease.[33] Sulphasalazine may be used for mild colonic disease and may be used in patients with joint symptoms. There may be a role for mesalazine in prevention of recurrence of post-operative Crohn's.[34]

Corticosteroids

Budesonide is first-line therapy for inducing remission of mild exacerbations of ileocaecal Crohn's disease.[35] It is associated with fewer adverse effects than systemic steroids such as prednisolone. Systemic steroids can be used for inducing remission during severe flares of ileocolonic Crohn's disease,[33] but anti-TNF drugs may be more appropriate. Steroids are not safe or efficacious for maintenance therapy.

Antibiotics, Probiotics, Prebiotics, and Faecal Transplantation

Ciprofloxacin and metronidazole are effective for treating septic complications of Crohn's disease and for perianal disease. The long-term sequelae of these two drugs include Achilles' tendon rupture and peripheral neuropathy, respectively. There is no convincing evidence that antibiotic therapy is effective in maintaining remission in Crohn's disease.[33,36] There are no data that probiotics, prebiotics or faecal transplantation provide any benefit in the treatment of Crohn's disease.

Immunomodulators

The thiopurines azathioprine and 6-mercaptopurine (6-MP) are widely used to maintain medically induced remission of moderate-to-severe Crohn's disease. Onset of action is slow, and full clinical response may take up to 16 weeks, therefore immunomodulators should not be used as single agent therapy, but should be used alongside a drug that induces rapid remission (e.g. corticosteroid or biological therapy). In patients who start to fail thiopurines therapy, thiopurine metabolites can be measured to ensure therapeutic dosing before considering a change in medication. Common adverse effects include nausea, vomiting, pancytopaenia, and pancreatitis. Mild-to-moderate drug side-effects would warrant a switch between thiopurine agents. A severe adverse reaction, such as acute pancreatitis, would be a contraindication to the further use of thiopurines. Methotrexate,

an anti-metabolite, is used in Crohn's disease. It is also effective at treating inflammatory bowel disease (IBD)-related arthropathy. Complications of drug treatment include nausea, bone marrow suppression, and fibrosis of the liver, lungs, and thyroid. Concomitant folic acid supplementation is important.

Anti-TNF Therapy

Monoclonal antibody therapy, including infliximab, adalimumab and certolizumab, is effective for induction and maintenance of remission of moderate-to-severe Crohn's disease.[37,38] Development of antibodies to the drug may impair efficacy, but incidence of antibody formation can be reduced by regular scheduled dosing[39] (as compared with ad hoc dosing) and by concomitant use of an immunomodulator.[29,40] Adverse effects of anti-TNF therapy include infusion reactions, local injection site reactions, demyelination, reactivation of latent infections (especially tuberculosis), and a potentially increased risk of malignancy. The absolute risk of lymphoma is 1.9/10,000 patient-years for a patient with Crohn's disease. With the addition of an immunomodulator the absolute risk is 3.6/10,000 patient-years, and with dual therapy (anti-TNF plus immunomodulator) the absolute risk is 6.1/10,000 patient-years.[41] In patients with no other risk factors for malignancy, the significant benefits of anti-TNF therapy may weigh favourably against this small increase in absolute risk. In patients with other risk factors for malignancy, especially past medical history and advancing age, the absolute risk is likely to be increased and the use of anti-TNF must be carefully considered.

New Agents

Natalizumab is a humanised monoclonal antibody against the cell adhesion molecule α4-integrin that has FDA approval. Therapies targeting inflammatory cytokines and homing molecules are also under investigation.

Surgery

Distal ileal resection can be considered for short segment moderate-to-severe disease. Extensive small bowel resection can lead to short bowel syndrome, and so intensification of medical therapy and trial of stricturoplasty are important to attempt to maintain bowel length. Surgery is also performed for perianal complications and includes laying open fistulae and seton insertion as well as drainage of abscesses.

PREGNANCY AND IBD

The highest peak of incidence of Crohn's disease is during the child bearing years, so questions about fertility, pregnancy, and breast-feeding are often asked by patients. Data suggest that whilst inactive Crohn's disease does not reduce fertility, active disease and previous abdominal or pelvic surgery are associated with decreased fertility. Patients with Crohn's disease have, on average, fewer children than healthy controls, but a large population-based trial showed that this is probably related to patient choice.[42]

The over-riding aim of therapy during pregnancy is to maintain remission. Active disease is associated with adverse pregnancy outcomes.[43,44] Steroids, 5-ASA, and azathioprine are probably safe in pregnancy,[45] but careful counselling of the family is important, and compliance should be encouraged through patient education. Anti-TNF therapy is also thought to be safe, although it does cross the placental barrier; if possible, doses should be avoided in the final trimester. Methotrexate and thalidomide are both highly teratogenic and are absolutely contraindicated in the period before conception (for the father as well as the mother) and during the pregnancy. Sulfasalazine is known to reduce sperm numbers and motility. Caesarean section should be considered for cases of active perianal disease.

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