Crohn's disease

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Abstract
Crohn's disease is one of the two main inflammatory bowel diseases, the other being ulcerative colitis. It is defined as a transmural inflammation of the bowel involving the terminal ileum and right colon preferentially, but also the small bowel, colon, rectum and the perineal area. The main symptoms are diarrhea, abdominal pain, weight loss often accompanied by extra digestive manifestations such as fever, aphtosis, arthralgia, erythema nodosa. Etiology is still unknown. However, Crohn's disease is thought to be the consequence of an hyperactivated intestinal immune system resulting from the action of unknown environemental factors on genetically-determined susceptibility. Its incidence is lower in Southern countries than in Northern countries (1 to 5 /100,000) as well as its prevalence (25 to 150 /100,000). The main drugs are salicylates, steroids, immunomodulators. Surgery is often required for treatment of bowel stenosis, abscess, internal fistula, as well as ano-perineal manifestations of the disease. Patients may require either enteral or parenteral nutrition.

Key-words
Crohn's disease; inflammatory bowel disease; diarrhea, abdominal pain; weight loss

Disease name and synonyms

Crohn's disease (CD);
granulomatous colo-ileitis;
regional enteritis.

Excluded diseases

Ulcerative colitis;
indeterminate chronic colitis;
microscopic colitis; collagenous colitis;
lymphocytic colitis; celiac disease;
functional intestinal disorders;
irritable bowel syndrome.

Diagnosis criteria/Definition

The diagnosis relies on the accumulation of various criteria including clinical, endoscopical, histological and biological findings.
The clinical manifestations depend on the distribution and severity of the disease, together with the presence of complications. The most

common symptoms are: diarrhea, abdominal pain, rectal bleeding, anorexia, weight loss.
They depend on the site of the disease (see table 1).

Table1 : Frequency of affected site in Crohn disease

Site	Frequency
Extensive small bowel disease	5%
Ileum only	25%
Ileocecal	40%
Colon only	25%
Miscellaneous (i.e confined to anorectum, oral, gastric)	2%

The main features in patients with small bowel disease are pain and weight loss. If it mainly occurs after meals, it may indicate partial intestinal obstruction. The prominent features in patients with colonic disease are diarrhea and bleeding.
CD may be revealed by surgical complications: complete or partial intestinal occlusion; intra-abdominal, pelvic, or perineal abscess, free peritoneal perforation.
Extra digestive manifestations may occur in parallel with the digestive symptoms during attacks such as fever, arthralgia, arthritis, buccal aphtosis, erythema nodosa, pyoderma gangrenosum, iritis, episcleritis.

Physical examination
The main features to look for are: oral aphtosis, abdominal tenderness and masses, anal tags, fissure and fistulae, nutritional deficiency. An important feature in children is growth retardation.

Endoscopy
Rigid or flexible procto-sigmoidoscopy will establish the diagnosis of Crohn's proctitis. Mild inflammation may consist of erythema, aphtous ulcers, granularity with increased contact bleeding but with intervals of preserved normal mucosa.
Colonoscopy helps to determine the pattern and severity of colonic and terminal ileum inflammation, and allows biopsies to be obtained. Endoscopic features are aphtous ulcers, deeper ulceration (sometimes spread like "geographical maps"), postinflammatory polyps (which indicate previous severe inflammation), but always accompanied by intervening normal mucosa, which is an important differential feature between CD and ulcerative colitis .

Biopsies
Rectal and colonic biopsies should be examined to find the nature of the inflammation (ulcerative colitis versus CD), collagenous colitis or microscopic inflammation if macroscopic appearance is normal, and infection. CD histology is characterized by preserved mucosal architecture, a deep inflammatory infiltrate toward the lamina propria, fissura, and pseudo-tuberculoid granuloma (found in only 20-30 % of patients with CD).

Radiology
In acute severe colitis, a plain abdominal radiograph is sufficient to diagnose the extent and severity of the attack. The colon may dilate (« toxic megacolon ») to a diameter superior to 8 cm. The presence of musocal islands indicates severe inflammation due to detached mucosa.
In long-standing CD, the colon may become tubular and shortened due to the loss of haustrations.
Small bowel enema is now the technique of choice for the barium examination of the small intestine; by his method, the extent of small bowel CD could be determined. The main features are: thickening and distortion of the valvulae conniventes, edema of the wall, ulcers and fissuring, luminal narrowing and strictures, prestenotic dilatation indicating severe stricture, fistulae to other abdominal organs or to the skin.

Blood tests
Anemia may be present due to blood loss (iron deficiency), chronic inflammation, or B12 malabsorption (macrocytic) in CD. Hypoalbuminemia suggests severe disease with denutrition.
The best markers of inflammation severity in CD are elevation of the C-reactive protein and platelet count.
Anti-saccharomyces cerevisiae antibodies (ASCA) are positive in 50-60% of CD patients while anti-neutrophil polynuclear antibodies (ANCA) are positive in 50-60% of UC patients. The combination ASCA+/ANCA- has a positive predictive value for the diagnosis of CD superior to 90%.

Differential diagnosis
Other conditions to consider if there is terminal ileal or colonic inflammation include:
Tuberculosis,
Bacterial infection Yersinia (if only the terminal ileum is inflamed),
Parasitic infection including amoebiasis or schistosomiasis if the patient has been to or comes from an endemic area,
Behçet's disase if there are deep punched-out ulcers.
Infection can also occur in patients with established IBD (Inflammatory bowel disease), and should be excluded by routine stool culture during new acute episodes of diarrheal illness.

Prevalence
It varies a lot depending on the geographic area, but it is constantly inferior to the prevalence of ulcerative colitis (except in France). It varies from 140/100,000 in Scandinavia, Great Britain, the USA, Canada to 50/100,000 in Southern Europe. In France, the prevalence is estimated to be 110 /100,000 in the year 2000.

Management including treatment

Drugs used in CD

Corticosteroids
Steroids are proved to be effective in acute attacks of CD. The optimum initial dose of oral prednisolone for acute episodes of inflammatory bowel disease (IBD) is 1 mg /kg /day in a single morning dose resulting in a control of symptoms in 60-80 % of patients in 2 to 4 weeks of treatment. Most patients tolerate well short courses of oral steroids, even at high doses, without major side effects including: weight gain, mood swings (insomnia), acne, easy bruising, hypertension, adrenal suppression. These effects can be reduced by weaning off the dose quickly as an acute episode is controlled. Long-term steroid use is associated with increased risk of bone necrosis (e.g. femoral head), osteopenia (with increased risk of vertebral collapse and other fractures). Every attempt should be made to conserve bone density in patients with CD, including preventive treatment with oral intake of calcium, vitamin D and diphosphonates.
Around 30 % of treated patients become corticodependent, i.e. they are controlled while under a 15-20 mg dose of prednisolone and relapse quickly when it is stopped. Steroids are not effective in maintaining remission and should not be used for prolonged periods.

New steroids
A recent therapeutic approach involves the use of steroids rapidly metabolized on first pass through the mucosa or liver. The systemic bioavailability after oral administration of budesonide (the only new steroid currently used) is about 10 %, which results in reduced steroids side effects. Budesonide (9 mg/day) has the same action than prednisolone 40 mg/day in the treatment of acute CD, with however, longer relapses and less side effects.

5-amino salicylic acid (5-ASA) compounds

Sulphasalazine
Sulphasalazine is the longest established 5-ASA compound (dose of 2 g/day). It contains 5-ASA linked to sulphapyridine by an azo bond, which is split by bacteria in the terminal ileum and colon. Its side effects (headache and nausea) occurring in 15 % of patients, are often dose-related.

Mesalazine or mesalamine
More recent 5-ASA (called mesalazine or mesalamine) compounds was used
They do not contain a sulphur component. They are just as effective as sulphasalazine and are better tolerated. Differences between compounds relate to the different mechanisms of mesalamine delivery:
Asacol® and Rowasa® contain mesalamine coated with a pH-sensitive acrylic polymer called Eudragit®-S which dissolves at the pH (pH 6-7) found in the terminal ileum and colon.
Pentasa® is another mesalamine compound that is slowly released and composed of microparticles coated with ethylcellulose. They are released throughout the small bowel and colon. A dose of 3-4 g/day is mildly effective in acute episodes when given orally. Rectal preparations are as effective as steroids in acute episodes of procto-sigmoiditis and in some patients they are more effective.
The great value of 5-ASA drugs is their ability to maintain remission in CD at a dose of 2-3 g/day, specially after surgical resection.
The 5-ASA drugs are rarely associated with nephrotoxicity due to interstitial nephritis.

Azathioprine and 6-mercaptopurine
Azathioprine is metabolized to 6-mercaptopurine in vivo. This drug is very useful for:
- *patients who have frequent relapses despite taking a 5-ASA compound,*
- *patients with chronic active disease,*
- *patients who are steroid-dependent.*

It is proved to be effective in 50-60% of patients with CD.
The optimum dose of azathioprine is 2 mg/kg/day and 1.5 mg/kg/day for 6-mercaptopurine, and at least 2-4 months of therapy are required for the drug to have its maximum effect (up to 6 months in some patients).
About 6 % of patients cannot tolerate the drug because of nausea or vomiting, flu-like syndrome, drug fever, or pancreatitis. To avoid leukopenia, a blood count should be done every 10 days in the first 3 months and every month thereafter. Falls in white cell count are reversible by stopping the drug.

Methotrexate
Methotrexate in an anti-metabolite folic-acid inhibitor with both immunosuppressant and anti-inflammatory activity and has the same indications as azathioproprine - 6-mercaptopurine. Its side effects include nausea, diarrhea, stomatitis, leukopenia, elevation of liver

function tests, pneumonitis, liver fibrosis (related to cumulative doses).
The dose which has been used in IBD is 25 mg intramuscularly once a week for short courses (12 weeks), followed by 7.5-15 mg orally per week. Up to 20 % of patients will have side effects which prevent its use. The beneficial effect of methotrexate is usually apparent within 2 to 4 weeks .
Blood counts and liver function tests should initially be performed every 10 days the first 3 months and then every month. The drug should be avoided when the risk of liver damage is increased. It is contraindicated to start a pregnancy during the treatment for the future father and mother, since it is a highly teratogenic drug.

Cytokine modulators
Tumor necrosis factor alpha (TNF-alpha) antibody (5 mg/kg) treatment has been shown to induce remission in two thirds of patients with CD resistant to standard therapies after a single infusion. It also induced 60 % improvement of severe anoperineal lesions after 3 infusions of 5 mg/kg each. The long-term side effects and benefits remain to be determined.

Nutritional therapies
They may be the main treatment or may be used in combination with drugs or surgery. Inadequate nutrition is a major cause of weight loss in adults and impaired growth in children and adolescents. Nutritional supplementation may be given orally or via nocturnal nasogastric feeding in children with growth problems or patients resistant to standard therapy.
Complete bowel rest by intravenous feeding is used in severe resistant or complicated diseases (internal fistula, bowel stenosis).
So far, there has been no specific daily oral diet effective in preventing flare up of Crohn's disease after remission. Food intake must be varied, abundant, the only limits being the tolerance and the tastes of the patient.

Surgical treatment
Surgery in CD is reserved for the complications of the disease or for active disease resistant to treatment. The main indications include: abscess that cannot be percutaneously drained, intestinal obstruction, enterocutaneous fistula, a limited segment causing severe symptoms despite treatment, perianal infection requiring drainage. Ileostomy or colostomy, most often transitory but sometimes definitive, may be required.

Etiology

Environmental factors

Smoking
Smoking increases the risk of developing CD and doubles the risk of postoperative recurrence, particularly in women.

Oral contraceptives
There may be a slight association between oral contraceptive use and the development of CD. This is insufficient to deny the oral contraceptive to a patient, unless she/he has had previous venothrombotic disease.

Infective agents
Despite much effort, incontrovertible evidence of an infective cause for CD has not emerged. The most studied agents have been measles virus, Mycobacterium paratuberculosis, and E Coli (endogenous flora).

Genetic factors
The genetic contribution to the etiology of CD is polygenic in pattern rather than simply Mendelian, it is stronger in CD than ulcerative colitis. Susceptibility loci on chromosomes 16, has been confirmed in different surveys of familial cases of CD leading to the discovery of three main mutations on gene NOD 2 in a subset of patients with CD.

Genetic counseling
There are no established guidelines for (IBD) risk to offspring of affected parents. The relative risk for a first-degree relative of a patient with CD to develop CD is 10-15 times higher than the one in general population. The lifetime risk to children of a parent with IBD ranges between 5 and 10%, half of the risk being reached during the third decade of life.

Antenatal diagnosis
not relevant

Unresolved questions
The main questions are:
- *the functional implication of the mutations on gene NOD2 which is recently discovered;*
- *identification of environmental factors and specially infectious agents, either exogenous or endogenous, playing a role in the pathophysiology of the disease;*
- *role of stress in CD;*
- *assessment of new "biological therapies" (specially new anti-cytokines), prebiotics, probiotics, antibiotics, combined treatments; search for new immunomodulators effective in preventing relapses on the long term.*

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