Crohn’s Disease

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Introduction

- Inflammatory disease of the intestines that may affect any part of gastrointestinal tract from mouth to anus

Definition:
- Crohn’s Disease is a chronic, relapsing and remitting inflammatory disease of the gastrointestinal tract, affecting any site from mouth to anus.
- Characterised by segmental transmural inflammation, and ‘skip lesions’.

Burrill Bernard Crohn, American Gastroenterologist, 1932

Also known as:
- Inflammatory bowel disease
- Regional ileitis or enteritis
- Granulomatous ileocolitis
Symptoms

• May cause wide variety of symptoms
• Main symptoms:
  • Abdominal pain
  • Diarrhoea +/- blood
  • Vomiting
  • Weight loss
• Complications outside GIT
  • Skin rashes
  • Arthritis
  • Liver disease
  • Inflammation of eye
Epidemiology

- Incidence: 6 - 7.1/100,000
- Prevalence: 27 – 48/ 100,000
- Can occur at any age but usually presents in teens and twenties
- 2\textsuperscript{nd} peak incidence in the fifties to seventies
- Males and females equally affected

- No known pharmaceutical or surgical cure
- Treatment aims:
  - \textit{To control symptoms}
  - \textit{Maintain remission}
  - \textit{Prevent relapse}.
Pathophysiology

• Autoimmune disease
  • Body's immune system attacks GIT causing inflammation

• Genetic component
  • Individuals with affected siblings at higher risk
  • Parents, siblings or children 3 to 20 times more likely
  • Twin studies show a concordance of greater than 55% for Crohn's disease.

• Environmental component
  • Higher number of cases in western industrialized nations
  • Smokers are two times more likely to develop Crohn's disease
Environmental Factors

• Diet
  • Higher prevalence in industrialized parts of the world
  • Positive correlation between incidence of disease and increased intake of animal protein, milk protein and an increased ratio of n-6 to n-3 polyunsaturated fatty acids
  • Negative correlation of the disease incidence was found to the increased consumption of vegetable protein

• Smoking
  • Increases risk of return of active disease, or "flares"

• Oral Contraceptive Pill
  • Introduction of hormonal contraception in USA in 1960s linked with dramatic increase in incidence rate
  • Causal linkage not been shown.
Microbes

- Microorganisms take advantage of their host's weakened mucosal layer and inability to clear bacteria from the intestinal walls
- *Mycobacterium avium subspecies paratuberculosis* (MAP) may play role, causes similar disease in cattle
- Specific strains of enteroadherent *E. coli* also linked
- Relationship between specific types of bacteria and Crohn's disease remains unclear.
Pathology

- Transmural inflammation;
- Enlargement of submucosal lymphoid follicles;
- Obstructive lymphoedema;
- Transverse and longitudinal ulceration of mucosa overlying lymphoid follicles (cobblestoning);
- End stage is fibrostenosing stricture.
Pathophysiology

- Transmural pattern of inflammation
- Inflammation may span entire depth of intestinal wall
- Ulceration seen in highly active disease
- Usually abrupt transition between unaffected tissue and ulcerated area
- Biopsies show mucosal inflammation characterized by focal infiltration of neutrophils into epithelium
- Occurs in area overlying lymphoid aggregates
- Neutrophils, along with mononuclear cells, may infiltrate into the crypts leading to inflammation (crypititis) or abscess (crypt abscess).
Pathophysiology

- Granulomas, aggregates of macrophage derivatives known as giant cells, are found in 50% of cases.
- Granulomas do not show "caseation", a cheese-like appearance on microscopic examination that characteristic of granulomas associated with infections such as tuberculosis.
Classification

- Categorized by area of gastrointestinal tract it affects:
  - *Ileocolic Crohn's disease* – 50%
    - Ileum and large intestine
  - *Crohn's ileitis* – 30%
    - Ileum only
  - *Crohn's colitis* – 20%
    - Large intestine,
    - Difficult to distinguish from ulcerative colitis.
  - *Gastroduodenal*
  - *Jejunoileitis*
    - Patches of inflammation in proximal small intestine.
Classification

- Also categorized by behaviour of disease

- Three categories:
  - **Stricturing**
    - Causes narrowing of bowel that may lead to bowel obstruction
  - **Penetrating**
    - Creates abnormal passageways (fistulae) between bowel and other structures
  - **Inflammatory** (non-stricturing, non-penetrating disease)
    - Causes inflammation without causing strictures or fistulae.
Gastrointestinal Symptoms

- May have symptoms for years prior to diagnosis
  - *Periods of flare-ups and remission*

- Abdominal pain may be initial symptom
  - *Vague, non specific, obstructive symptom*
  - *Flatulence and bloating*

- Diarrhoea
  - *Up to 20 per day*
  - *May need to awaken at night to defecate*
  - *May or may not be bloody – more likely colitis*
  - *Consistency may range from solid to watery.*
  - *Nature of diarrhoea depends on part of small intestine or colon involved*
  - *Ileitis typically results in large-volume watery faeces.*
Gastrointestinal Symptoms

• Perianal discomfort common
• Itchiness or pain around the anus suggestive of inflammation, fistulization or abscess or anal fissure
• Perianal skin tags also common
• Faecal incontinence may accompany peri-anal Crohn's disease
• Mouth may be affected by non-healing sores (aphthous ulcers)
• Rarely, oesophagus and stomach involved
• Symptoms including difficulty swallowing (dysphagia), upper abdominal pain, and vomiting.
Diagnosis

- Sometimes challenging
- Number of tests often required
- May not be possible to diagnose with complete certainty
- Colonoscopy approximately 70% effective
- Further tests less effective
- Disease in small bowel particularly difficult to diagnose
- Capsule endoscopy aids in endoscopic diagnosis
- Biopsy: Multinucleated giant cells, common finding in lesions of Crohn's disease
Blood Tests

• Full Blood Count
  • Anaemia
    • Caused either by blood loss or by vitamin $B_{12}$ deficiency (vitamin $B_{12}$ not absorbed in ileitis)
  • White cell count
• Erythrocyte sedimentation rate, or ESR
• C-reactive protein
  • Gauge the degree of inflammation
• Liver Function Tests
Endoscopy

- Colonoscopy best test for making diagnosis
- Allows direct visualization of colon and terminal ileum
- 30% of Crohn's disease involves only ileum, cannulation of terminal ileum required in making diagnosis
- Patchy distribution of disease, with involvement of colon or ileum but not rectum, suggestive of Crohn's disease
Radiological Investigations

• Barium Small bowel follow-through X-ray
  • *Barium sulfate suspension drink*
  • Fluoroscopic images of bowel taken over time
  • Useful for looking for inflammation and narrowing of small bowel

• Barium enema
  • *Barium inserted into rectum*
  • Fluoroscopy used to image bowel
  • Rarely used due to colonoscopy
  • Useful for identifying colonic strictures or colonic fistulae

• CT and MRI scans
  • Useful for evaluating the small bowel
  • Also for intra-abdominal complications such as abscesses, small bowel obstruction, or fistulae.
Radiological Investigations

- Thickened folds (oedema)
- String sign (tubular narrowing due to spasm or stricture depending on chronicity)
- Mucosal ulcers (apthous ulcers or deeper transmural ulcers)
- Sinus tracts and fistulae
Radiological Investigations

- Barium Small bowel follow-through X-ray
  - Inflammation and narrowing of small bowel
  - Partial obstruction (bowel wall oedema and luminal narrowing or scarring causing fibrostenotic strictures).
Radiological Investigations

- Barium enema
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Radiological Investigations

- Thickened folds (oedema)
- Sinus tracts and fistulae
- Inflammation of surrounding mesentery (creeping fat) with possible abscess formation
- Partial obstruction (bowel wall oedema and luminal narrowing or scarring causing fibro-stenotic strictures).
Treatment

• Currently no cure for Crohn's disease

• Remission may not be possible or prolonged if achieved

• Risk of relapse reduced and symptoms controlled with medication, lifestyle changes and in some cases, surgery.

• Treatment only when symptoms are active and involve first treating acute problem, then maintaining remission.
Lifestyle Changes

• Certain lifestyle changes can reduce symptoms:
  • Dietary adjustments – low dietary fibre diet
  • Elemental diet
  • Proper hydration
  • Smoking cessation.
Medication

• Acute treatment:
  • Medications to treat any infection (normally antibiotics) and
  • Reduce inflammation (normally aminosalicylate anti-inflammatory drugs and corticosteroids).

• When symptoms in remission, treatment enters maintenance with a goal of avoiding recurrence of symptoms.

• Prolonged use of corticosteroids has significant side-effects

• Alternatives include:
  • Aminosalicylates alone
  • Immunosuppressive drugs
Medication

- Medications used include:
  - 5-aminosalicylic acid (5-ASA) formulations
  - Prednisone
  - Immunomodulators:
    - Azathioprine
    - Mercaptopurine
    - Methotrexate
  - Biological medications:
    - Infliximab
    - Adalimumab
    - Certolizumab
    - Natalizumab
  - Intravenous Hydrocortisone in severe acute attack.
Complications

- Mechanical intestinal complications:
  - Obstruction
  - Fistulae
  - Abscesses
  - Free perforation
  - Haemorrhage.

- Obstruction typically occurs from strictures or adhesions that narrow lumen

- Fistulae can develop between:
  - Two loops of bowel  Enteroenteral fistula
  - Bowel and bladder  Colovesical / Enterovesical fistula
  - Bowel and vagina  Colovaginal / Enterovaginal fistula
  - Bowel and skin.  Colocutaneous / Enterocutaneous fistula

- Abscesses: a collections of pus, can occur in abdomen or in perianal area.
Complications

- Increased risk of cancer in area of inflammation
- Small bowel Crohn's at higher risk for small intestinal cancer
- Crohn's colitis relative risk of 5.6 for developing colon cancer
- Screening with colonoscopy recommended if Crohn's colitis > 5 years
Surgery – Main Indications

• Perianal disease
  • Abscess drainage
  • Fistula management – Insertion of Seton
  • Anal fissures

• Terminal ileal disease – Ileocaecotomy / Right Hemicolecetomy
  • Right iliac fossa mass
  • Stricture
  • Perforation

• Acute colitis / Toxic megacolon
  • Subtotal colectomy
  • Ileorectal anastomosis
Ischiorectal Abscess

• Examination Under Anaesthetic
  • Incision and Drainage
  • Incision and tube drainage
Anal Fistula

Suprasphincteric Fistula
Extrasphincteric Fistula

Surgery: Examination Under Anaesthetic (EUA)

- Insertion of Seton
- Laying open
  - Risk of incontinence
Anal Fistula
Anal Fissure

• If failure of medical therapy:
  • Examination Under Anaesthetic (EUA)
    • *Injection of Botulinum toxin*
    • *Lateral Internal Sphincterotomy*
Surgery

- Surgery required for complications:
  - Obstructions
  - Fistulas
  - Abscesses
  - Failure to respond to drugs

- Laparoscopy / Laparotomy
  - May recur at site of resection / anastomosis
  - After first resection, further resection may be necessary within five years
Surgery

• For obstruction due to stricture, two options for treatment available:
  • \textit{Strictureplasty}
  • \textit{Segmental bowel resection}

• Re-operation rates 31\% and 27\%, respectively, indicating that strictureplasty is a safe and effective.
Surgery

• Terminal ileal disease – Ileocaecotomy / Right Hemicolecctomy
  • *Right iliac fossa mass*
  • *Stricture*
  • *Perforation*
Surgery

- For Acute Colitis:
  - Subtotal Colectomy with end ileostomy – Leave Rectum in situ

- When patient recovered – Ileo-rectal anastomosis

- Complications
  - Rectal disease / surveillance
Surgery

- For Pan colitis
- Proctocolectomy and end Ileostomy
- If anal sphincter left in situ, reconstruction possible
Surgery

- Ileal Pouch Anal Anastomosis
- (Restorative proctocolectomy)
- Best outcome
  - 4-6 motions per day
  - No night-time defaecation

- Complications
  - Failure
  - Pouchitis
  - Short bowel syndrome
Surgery

• By 20\textsuperscript{th} year of onset of symptoms, approximately 75% have surgery

• High rate of disease recurrence after segmental bowel resection

• Principle of surgery is preservation of intestinal length and function

• Guidelines for those requiring surgery include:
  • Persistent symptoms despite high-dose corticosteroids
  • Treatment-related complications including intra-abdominal abscesses
  • Medically intractable fistulae
  • Fibrotic strictures with obstructive symptoms
  • Toxic megacolon
  • Haemorrhage
  • Cancer
Surgery

- Short bowel syndrome caused by surgical removal of small intestines
- Develops if > half or more of small bowel removed
- Diarrhoea main symptom, other symptoms may include cramping, bloating and heartburn
- Short bowel syndrome treated with changes in diet, intravenous feeding, vitamin and mineral supplements and treatment with medications
- Removal of terminal ileum may lead to excessive watery diarrhoea
- Due to inability to reabsorb bile acids after resection of terminal ileum
Prognosis

• Appropriate medical and surgical therapy helps patients have reasonable quality of life
• Medical therapy becomes less effective with time
• Surgery for underlying complications required in ~ 66%
• Mortality rate increases with duration of disease

• GI tract cancer is the leading cause of disease-related death:
  • Colorectal
  • Small bowel adenocarcinoma
  • Lymphomas
  • Squamous cell carcinomas arising in chronic fistula to skin.
Mortality/Morbidity

- Usually chronic, indolent course regardless of site of involvement
- Estimated ranges from no increased risk to up to a 5-fold increased risk of death
- Mortality highest in first 4-5 years after diagnosis
- In first year after diagnosis, relapse rate approaches 50%, with 10% having chronic relapsing course
- 15-year survival rate is 93.7% of the general population
- 10% of patients will be disabled by their disease

- Chance of death and complications increases with duration of illness
- Patients with proximal small bowel disease have higher risk of mortality compared with ileal or ileocaecal disease
Extra-intestinal Manifestations

• Skin:
  • Erythema nodosum
  • Pyoderma gangrenosum

• Joints:
  • Arthritis
  • Ankylosing spondylitis
  • Sacroiliitis

• Eyes:
  • Episcleritis
  • Iritis
  • Uveitis

• Liver and biliary system:
  • Pericholangitis
  • Sclerosing cholangitis
  • Autoimmune hepatitis
  • Cirrhosis.
Pyoderma gangrenosum

- Skin lesion typically a painful ulcerating nodule.
Erythema Nodosum

- Presents as red nodules usually appearing on back
- Due to inflammation of underlying subcutaneous tissue and is characterized by septal panniculitis.
Ankylosing spondylitis

- Greek *ankyllos*, bent; *spondylos*, vertebrae
- Chronic, inflammatory arthritis and autoimmune disease
- Mainly affects joints in spine and sacroilium in pelvis
- Can cause eventual fusion of spine.
Arthritis

• Symptoms:
  • Painful, warm, swollen, joints
  • Stiff joints
  • Loss of joint mobility or function.
Comparison with Ulcerative Colitis

• Ulcerative colitis similar symptoms of Crohn's disease

• Both are inflammatory bowel diseases that affect the colon

• Course of diseases and treatments may be different.

• In some cases, not be possible to differentiate, in which case the disease is classified as indeterminate colitis.
Comparisons of various factors in Crohn's disease and Ulcerative Colitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal ileum involvement</td>
<td>Commonly</td>
<td>Seldom</td>
</tr>
<tr>
<td>Colon involvement</td>
<td>Usually</td>
<td>Always</td>
</tr>
<tr>
<td>Rectum involvement</td>
<td>Seldom</td>
<td>Usually</td>
</tr>
<tr>
<td>Involvement around the anus</td>
<td>Common</td>
<td>Seldom</td>
</tr>
<tr>
<td>Bile duct involvement</td>
<td>No increase in rate of primary sclerosing cholangitis</td>
<td>Higher rate</td>
</tr>
<tr>
<td>Distribution of Disease</td>
<td>Patchy areas of inflammation (Skip lesions)</td>
<td>Continuous area of inflammation</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Deep geographic and serpiginous (snake-like) ulcers</td>
<td>Continuous ulcer</td>
</tr>
<tr>
<td>Depth of inflammation</td>
<td>May be transmural, deep into tissues</td>
<td>Shallow, mucosal</td>
</tr>
<tr>
<td>Fistulae</td>
<td>Common</td>
<td>Seldom</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Common</td>
<td>Seldom</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Widely regarded as an autoimmune disease</td>
<td>No consensus</td>
</tr>
<tr>
<td>Cytokine response</td>
<td>Associated with $T_h 17$</td>
<td>Vaguely associated with $T_h 2$</td>
</tr>
<tr>
<td>Granulomas on biopsy</td>
<td>May have non-necrotizing non-peri-intestinal crypt granulomas</td>
<td>Non-peri-intestinal crypt granulomas not seen</td>
</tr>
<tr>
<td>Surgical cure</td>
<td>Often returns following removal of affected part</td>
<td>Usually cured by removal of colon</td>
</tr>
<tr>
<td>Smoking</td>
<td>Higher risk for smokers</td>
<td>Lower risk for smokers</td>
</tr>
</tbody>
</table>