Inflammatory bowel disease is an umbrella term for two conditions — ulcerative colitis and Crohn’s disease. Although these affect the bowel, up to 40% of sufferers experience extraintestinal symptoms.

Inflammatory bowel disease
clinical features and diagnosis

By Sampath De Silva, MBBS, MRCP

The term “inflammatory bowel disease” (IBD) encompasses ulcerative colitis (UC) and Crohn’s disease (CD). Both are conditions characterised by relapsing intestinal inflammation with associated extraintestinal features. UC was the first of the two conditions to be described formally (by British physician Samuel Wilks in 1859); however, patients with non-infectious diarrhoea were described by the Roman physician Aretaeus as far back as 300 AD. CD was first described early in the 20th century by several different physicians. American gastroenterologist Burrill Crohn subsequently cited some of these reports and identified the characteristic finding of terminal ileitis in 1932. The cause of both conditions is multifactorial with both genetic and environmental factors believed to play a part.

Epidemiology

In the western world, the incidence of IBD has increased over the past century, particularly so in recent decades. The annual incidence of UC rose from 3.8/105 to 9.6/105 in Italy between 1978 and 1992, and 9.2/105 to 13.4/105 in Scandinavia between the 1980s and 2003. Likewise, the annual incidence of CD increased over the same periods from 1.9/105 to 3.4/105 in Italy, and 4.1/105 to 8.6/105 in Scandinavia. In 1993, the aggregated annual incidence in Europe was 10.4/105 for UC and 5.6/105 for CD. In recent years the incidence of CD has continued to increase, but that of UC has plateaued in several European countries.

There seems to be an increased prevalence of IBD in northern Europe and North America, with Caucasian people predominantly affected. Recent data show that the incidence of IBD has increased in Asia but the prevalence is still not as high as in Europe or North America.

The usual age of onset of IBD is 15 to 35 years. Onset under the age of 10 years is uncommon. Women have a 20–30% higher risk of developing CD than men, but the risk of developing UC is similar in men and women.

Causes

IBD is thought to be caused by inappropriate and ongoing activation of the mucosal immune system in the gastrointestinal tract (see Figure 1, p74) in the presence of normal luminal flora. This response is probably due to defects in the barrier function of the mucosal epithelium and the mucosal immune system.

Several causes for these defects have been investigated and are outlined below; however, no single cause of IBD has been identified.

SUMMARY

Inflammatory bowel disease (IBD) is a term that encompasses both ulcerative colitis (UC) and Crohn’s disease (CD). In UC inflammation affects the colon and the rectum; inflammation is limited to the bowel mucosa and can include oedema, ulceration and haemorrhage. Patients with UC usually present with blood and mucus in the stools and abdominal pain.

CD can affect any part of the gastrointestinal tract. There might be areas of normal gut interdispersed with areas of disease and the inflammation can affect the full thickness of the bowel. The clinical features of CD are more varied than those of UC and can include vomiting, diarrhoea, weight loss and abdominal pain.

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Genetics Genetic factors contribute to a person’s susceptibility to develop IBD. Studies show that first degree relatives of people with IBD are two to 20 times more likely to develop IBD than the background population; the absolute risk of developing IBD for first degree relatives is about 7%. There is a higher rate of disease concordance in monozygotic compared with dizygotic twins (particularly for CD).

Several candidate genes have been studied over the past two decades, including genes that affect cell signalling and inflammatory responses. Analysis of DNA from families in which there are members with IBD has identified an area on chromosome 16 that is linked to the incidence of CD. Subsequently this area was identified as the NOD2 gene. However, the exact mechanism by which polymorphisms in this gene confer an increased risk of CD is unknown. The polymorphisms of the gene are present in 30% of patients with European ancestry — being heterozygous for a polymorphism increases the risk of CD by a factor of 1.75–4 and being homozygous gives a 11–27-times higher risk.

Genetic associations between the interleukin 23 receptor gene and IBD, psoriasis and ankylosing spondylitis have been noted. It is believed that raised interleukin 23 and Th17 cytokines contribute to intestinal inflammation as seen in IBD. Although genetic factors have been identified, there is no confirmed pattern of inheritance — twin studies only show 45% concordance. This indicates that the cause of IBD is multifactorial, with both genetic and environmental factors playing a part.

Environment Environmental risk factors have been explored extensively as potential contributing factors to the development of IBD; the increased prevalence in certain geographical areas adds weight to the argument that environmental factors play a part.

Smoking A paradoxical relationship exists between smoking and IBD. Meta-analyses have shown that active smokers are less likely to develop UC than ex- or non-smokers. However, the opposite association exists for CD — active smokers, followed by ex-smokers, have increased risk of the disease. The mechanisms for these associations have not been identified.

Contraceptive pill The use of the oral contraceptive pill has been suggested to increase the risk of CD, but not UC. This may be due to immune enhancement or microvascular infarction due to oestrogen.

Appendectomy Appendectomy is associated with a decreased incidence of UC (particularly when appendectomy was performed before the age of 10 years); there is no correlation of note between appendicitis and CD. The precise mechanism for this disparity is unknown, but it is believed to relate to differences in the helper T-cell responses between patients with UC and CD.

Antibiotics The use of antibiotics in childhood has been associated with an increased risk of IBD, possibly due to interference with the development of normal tolerance to enteric bacteria.

Non-steroidal anti-inflammatory drugs There is a relationship between the use of non-steroidal anti-inflammatory drugs and an increased incidence risk of both UC and CD. It is believed that this effect is through the inhibition of prostaglandins and the immunoregulatory effect of NSAIDs.

Diet Diet has been shown to have an effect on the development of IBD. Studies have shown a twofold increase in the incidence of IBD among people who have a high sugar and fat diet. Studies into the association of mono- and polyunsaturated fats, long chain omega-3 fatty acids and fibre consumption with IBD have not revealed any consistent findings.

Infection Many micro-organisms have been considered as possible causes of IBD. Mycobacterium avium paratuberculosis (MAP) has been suggested as a possible cause of CD; MAP causes Johne’s disease (granulomatus ileitis) in ruminants (eg, cattle), which is similar to CD. Despite this, no firm association between MAP and CD has been identified.

The measles virus has been explored as a potential causative agent for CD but there is no evidence of a significant association between the two. Helminth infection appears to be inversely correlated with the incidence of IBD via immunoregulatory effects. Adherent-invasive Escherichia coli (AIEC) has been shown to be associated with CD, possibly via impaired clearance of the bacteria from the terminal ileum, especially in patients with NOD2 gene variants, leading to ongoing inflammation.

It has been suggested that other pathogens such as Salmonella, Campylobacter, Listeria and Yersinia spp could contribute to the development of IBD, but there is no conclusive evidence to support this.
Clinical features

In UC, bowel inflammation involves the colon and rectum (see Figure 1, p74). Inflammation is limited to the bowel mucosa, with oedema, ulceration and haemorrhage occurring in a confluent pattern. Histological findings show inflammation of the mucosa with polymorphonuclear leucocytes, mononuclear cells and depletion of goblet cells.

The main presenting features of UC are blood and mucus in the stools, with associated abdominal pain, particularly on defecation. With severe inflammation, patients may experience abdominal distension and rebound tenderness, which reflects a markedly increased risk of developing toxic megacolon (see Box 1).

CD can involve any part of the gastrointestinal tract from the mouth to the anus. There may be areas of normal digestive tract between the affected areas; the phrase “skip lesions” was coined to describe the distribution of bowel lesions. Inflammation can involve the full thickness of the bowel wall and lead to the formation of fistulas (e.g., between two loops of bowel or between the bowel and the bladder). Chronic submucosal inflammation can lead to the formation of non-caseating granulomas (nodular collections of inflammatory cells without cell necrosis) and strictures (areas of narrowing). CD most commonly affects the ileocaecal junction and terminal ileum (see Figure 1, p74).

The manifestations of CD are more varied than those of UC, which reflects the range of sites that can be affected:

- Upper-gastrointestinal tract — features include dysphagia, vomiting, nausea and epigastric pain
- Small bowel — tends to cause abdominal pain, weight loss, diarrhoea and anorexia
- Colon — presentation may be similar to UC
- Perianum — including skin tags, perianal fistulas and abscesses

Extraintestinal symptoms Extraintestinal symptoms are seen in both CD and UC, about 40% of patients with IBD have extraintestinal features including:

- Arthopathy — occurs in 4–23% of patients with IBD activity
- Eye effects — occur in 4–12% of patients with IBD; uveitis and iritis are more common in UC and episcleritis is more common in CD
- Mucocutaneous lesions — mouth ulcers can occur and reflect underlying disease activity
- Skin effects — erythema nodosum (characterised by raised, tender, red/purple skin lesions, which are about 1–5cm in diameter and commonly affect the extensor surfaces of the extremities) is more common in CD and reflects underlying disease activity, improvement coincides with improvement of bowel disease; pyoderma gangrenosum (deep, severe ulceration of the skin) is uncommon but more likely to be seen with UC
- Fever — present in 40% of patients with IBD at the time of presentation

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>CROHN’S DISEASE</th>
<th>ULCEERATIVE COLITIS</th>
</tr>
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<tbody>
<tr>
<td>Diarrhoea</td>
<td>Mild to severe</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Stools</td>
<td>Steatorrhoea (small intestine affected); visible or occult blood (sigmoid colon or rectal disease); occasional constipation (usually due to obstruction)</td>
<td>Blood, mucus, pus</td>
</tr>
<tr>
<td>Usual site</td>
<td>Mostly terminal ileum and ascending colon, but possible anywhere in the gut</td>
<td>Colon only, rectum is usually involved</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>Normal, or patchy ulceration</td>
<td>Always diffusely inflamed or ulcerated</td>
</tr>
<tr>
<td>Gut wall</td>
<td>Full-thickness involvement</td>
<td>Mucosa and submucosa only</td>
</tr>
<tr>
<td>Extraintestinal abdominal features</td>
<td>Yes (fatty liver, renal stones, adhesions)</td>
<td>No</td>
</tr>
<tr>
<td>Fistulas</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Onset</td>
<td>Insidious or acute</td>
<td>Usually insidious, occasionally sudden and severe</td>
</tr>
<tr>
<td>Pain</td>
<td>Colicky, may mimic appendicitis</td>
<td>Lower abdominal discomfort; moderate-to-severe attack is accompanied by systemic symptoms (e.g., fever, tachycardia)</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Perianal abscesses</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Raised erythrocyte sedimentation rate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Complications</td>
<td>Gallstones; perianal and internal fistulae; eyes; joints; skin; spine; fatty liver; renal stones; adhesions</td>
<td>The same as Crohn’s disease, but without gallstones, fistulas or renal stones</td>
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</tbody>
</table>
Weight loss — often seen in patients with IBD and is a result of anorexia or impaired absorption

Hepatobiliary disorders — occur in 5–15% of patients with IBD; primary sclerosing cholangitis (PSC) is usually associated with UC rather than CD and is characterised by fibrosing inflammation and obliteration of bile ducts; PSC may precede symptoms of IBD by several years and it increases the risk of biliary and colorectal cancers

**Diagnosis**

In addition to the symptoms above, the diagnosis of IBD also relies on investigational findings.

**Stool samples** Stool assays are important in excluding an infective cause of the patient’s symptoms. Faecal markers, especially leucocyte products, are raised due to bowel inflammation and (in the absence of infection) may indicate IBD. Faecal calprotectin and lactoferrin are two markers that have been investigated and shown to correspond with intestinal inflammation.

**Blood tests** A full blood count may reveal leucocytosis, microcytic anaemia and thrombocytosis for a patient with active IBD. Acute phase reactants such as the erythrocyte sedimentation rate and C-reactive protein would be expected to be raised if there was a process of ongoing inflammation. However, this elevation is usually less marked in UC (unless the colitis is severe).

Serological markers such as anti-Saccharomyces cerevisiae antibody (ASCA), and perinuclear antineutrophil cytoplasmic antibody (p-ANCA) can help confirm a diagnosis.

**Endoscopy** Colonoscopy or flexible sigmoidoscopy findings in IBD can vary. Findings in UC range from silent disease through erythema, fragile mucosa and erosions to, in the most extreme cases, severely haemorrhagic and ulcerated colon (see Figure 2 and Figure 3).

In CD, discontinuous involvement (skip lesions) might be seen, as may perianal lesions, a cobblestone appearance and deep ulceration. Full colonoscopy and ileoscopy are useful in obtaining terminal ileal biopsies to confirm CD histologically.

**Radiological tests** Abdominal X-ray is the initial investigation for patients with severe symptoms. This is to assess for toxic dilation of the bowel and also to see changes associated with colitis (eg, thickened large bowel wall and no faecal matter visible). To assess the extent of disease, particularly in CD, radiological investigations complement endoscopy.

Computed tomographic enterography and magnetic resonance imaging enterography have recently superseded fluoroscopic investigations because of improved sensitivity and specificity in detecting manifestations of CD.

**References**