Paediatric Inflammatory Bowel Diseases — brief update on current practice and future perspectives

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Abstract

Inflammatory Bowel Diseases (IBD) are chronic disorders of the digestive tract that result in relapsing inflammation of the intestinal mucosa. Over the last few decades we have seen a significant increase in the incidence of these conditions. This increase has been particularly noticeable in children and young adults, who currently contribute almost 30% of all patients diagnosed with IBD. Despite major advances in our knowledge, the exact cause of IBD remains unknown and in the absence of a curative treatment patients are still faced with a lifelong disabling condition. In the following brief review we will summarise current practice in diagnosing and managing children with IBD and highlight some of the recent advances. Additionally, we will briefly discuss ongoing research in the field and introduce epigenetics as a novel concept with a potential to explain some of the missing links in IBD disease pathogenesis.

Keywords biologics; Crohn's Disease; disease pathogenesis; epidemiology; epigenetics; infliximab; Paediatric Inflammatory Bowel Disease; Ulcerative Colitis

Introduction

Inflammatory Bowel Diseases (IBD) are chronic inflammatory disorders of the gut, with disease onset ranging from early childhood to beyond the sixth decade of life. The two main entities are Crohn's Disease (CD) and Ulcerative Colitis (UC). While in the latter inflammation is generally restricted to the mucosa of the large bowel, CD can spread throughout the entire gastrointestinal (GI) tract and affects all layers of the bowel wall (i.e., trans-mural inflammation). A third entity covers patients whose diagnostic features do not fully qualify for either CD or UC and are therefore diagnosed with IBD-unclassified (IBD-U).

The incidence of IBD is rising worldwide, with a particularly remarkable increasing trend in children. Currently, up to 30% of IBD patients are diagnosed during childhood or early adulthood. In the absence of any curative treatment, patients are faced with a lifelong, often severely disabling condition.

In the following short review we will summarise recent epidemiological data, general principals of diagnosing IBD and current treatment options available. We will finish with the introduction of epigenetics as a novel framework, which may provide some of the missing links in our current understanding of IBD disease pathogenesis.

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Epidemiology

The incidence of IBD is increasing worldwide, and IBD currently affect approximately one person in every 250 in the UK. Although patients can be diagnosed with IBD at any age, peak incidences are observed in childhood, between 10 and 15 years, and early adulthood (i.e., second-third decades of life). The gender distribution is equal. Interestingly, the incidence and prevalence of childhood onset IBD appear to have almost doubled over the last decade. IBD primarily affects the western world. The highest incidence rates are observed in North America (prevalence: 319 per 100,000 for CD, 249 per 100,000 for UC; incidence: 20.2 per 100,000 persons per year for CD and 19.2 per 100,000 persons per year for UC) and Europe (prevalence: 322 per 100,000 for CD, 505 per 100,000 for UC; incidence: 12.7 per 100,000 persons per year for CD and 24.3 per 100,000 persons per year for UC). However, a rapid increasing trend has been noted in developing countries adopting a westernized lifestyle such as India, China and Taiwan. One may hypothesise that these findings potentially reflect the major impact of our modern, "western" lifestyle on disease pathogenesis and we will come back to this at the end of the article.

In the UK, recent studies indicate an incidence of paediatric IBD of 5.2 per 100.000, with numbers dividing into 3.1 CD, 1.4 UC and 0.6 IBD-U cases. The disease distribution by gender showed a slight male preponderance (1.5:1) in CD patients before puberty, whereas a female preponderance was reported in adults. According to current estimates approximately 115,000 suffer from CD in the UK.

Clinical presentation

The clinical presentation of childhood IBD is highly variable and symptoms can be subtle. However, there are a number of classical symptoms and some important red-flags that should raise the suspicion of IBD in children and warrant further investigations.

Symptoms of CD commonly include chronic diarrhoea (longer than 6 weeks), abdominal pain and/or weight loss and these are seen in about 70% and 60% respectively of adult and paediatric patients before diagnosis. Systemic symptoms of malaise, anorexia, or fever are also frequently associated. Chronic non-specific symptoms can be indistinguishable from irritable bowel syndrome (IBS) and hence sometimes delay diagnosis. Unexplained anaemia and growth failure in children are clear red-flags and should therefore always be investigated further. Similarly, blood and/or mucus in the stools may be seen in up to 40%–50% of patients with CD and always require further investigations. Extra-intestinal manifestations (EIMs) are common in CD patients and may even be present prior to the onset of gastrointestinal symptoms. Abnormalities of the musculoskeletal system (such as sacro-ileitis, ankylosing spondylitis, peripheral arthritis) are the most common EIMs of IBD. Perianal fistulas are present in 10% of patients at the time of diagnosis, and may be the presenting complaint.

A clinical suspicion of UC arises in patients presenting with bloody diarrhoea, tenesmus and abdominal pain. Nocturnal

defaecation is also frequently reported. Systemic symptoms of malaise, anorexia, or fever are features of severe disease. Anal and minor perianal lesions may complicate severe diarrhoea, but recurrent or complex perianal fistulae would suggest a diagnosis of CD rather than UC. EIMs in UC include arthropathy, episcleritis and erythema nodosum and may accompany the presentation in about 10%; they rarely precede intestinal symptoms. An important EIM in patients with UC is primary sclerosing cholangitis (PSC). Hence, elevated liver enzymes combined with GI symptoms are highly suspicious of UC.

Although the majority of children will present with at least one of the above mentioned more "classical symptoms" including at least one of the "red-flags", IBD can sometimes present with very subtle symptoms such as unexplained anaemia or mild, chronic abdominal pain. Hence, once symptoms have been ongoing for a significant period of time, referral to a tertiary paediatric gastroenterology centre should be considered for further investigations.

Diagnostic work-up of IBD

Despite significant advances in the diagnostic tools available to date, the most important cornerstone of diagnosing IBD in children remains a thorough history, clinical examination followed by focused investigations. The diagnostic approach is summarised in Table 1. A final diagnosis is then made accordingly taking all aspects into consideration including clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Importantly, as mentioned above, given the variable clinical presentation combined with sometimes rather mild symptoms, the threshold to perform basic investigation should be low. However, not every child suffering from chronic abdominal pain requires endoscopic assessment as part of the diagnostic work-up.

Clinical history

A detailed medical history should include questioning about the onset of GI symptoms, including abdominal pain, and colitic symptoms i.e., recurrent episodes of rectal bleeding or bloody diarrhoea, urgency, tenesmus, incontinence and nocturnal diarrhoea. Weight loss and impaired energy levels should also be addressed. The family history should be also investigated, focusing on IBD and other immune-mediated conditions (e.g., auto-immune thyroiditis, diabetes, arthropaties).

Recent travels and contact with enteric infectious illnesses represent an important piece of information, aimed not only to differentiate infectious colitis, but also to detect any recent infection which might have subsequently triggered IBD. Food intolerance, ongoing medication (including antibiotics and non-steroidal anti-inflammatory drugs) are also important clues for differentiation.

Questioning about features of EIMs (involving the mouth, skin, eye, joints, or liver) and about perianal issues (e.g., episodes of perianal abscess or anal fissure) is also recommended as part of a detailed and complete history (Table 1).

Investigations

Blood based tests and serum markers: initial testing aims to detect signs of acute and/or chronic inflammatory response, anaemia, fluid depletion, and signs of malnutrition or malabsorption. At the time of presentation, serum inflammatory markers are generally higher in CD compared with UC. Blood inflammatory markers in children with active colitis may be normal, especially in mild disease.

Stool based investigations: a stool sample should always be sent for culture to rule out potential infectious causes. More recently, faecal inflammatory markers have been developed and are now

Milestones of the diagnostic work-up for paediatric IBD

Full history	• Familial predisposition for GI or immune disorders • Food allergies • Immunizations • Appendicectomy • Smoke exposure • Recent travels • Recent infectious gastroenteritis • Ongoing medication (e.g., antibiotics or non-steroidal anti-inflammatory drugs) • Onset of symptoms • Type, duration and severity of symptoms • Nocturnal symptoms • Perianal signs and symptoms (e.g., pain, discharge) • Extraintestinal symptoms (e.g., joint paint, pruritus, skin or eye conditions)
Clinical examination	• General well/being, pulse rate, blood pressure, temperature • Wt, Ht, BMI • Nutritional status (skin folds, muscular-fat mass) • Abdominal tenderness or distension, palpable masses • Oral inspections (aphthae) • Perianal inspection (skin tags, fissures, fistulae, abscesses) • Rectal digital examination • Check for EIMs e.g., involvement of liver (hepatomegaly, jaundice, pruritus), eye (epi-scleritis, uveitis), skin (erythema nodosum, pyoderma gangrenosum) and/or joints (axial or peripheral arthropathy)
First-line blood and stool tests	• Full blood count • Inflammatory markers (CRP, ESR) • Albumin • Liver function tests (ALT, AST, GGT, bilirubin) • Faecal biomarkers (e.g., faecal calprotectin, lactoferrin, or S100A12) • Stool cultures (e.g., CMV, Clostridium Difficile)
Disease activity scores	• PCDAI • PUCAI

BMI = Body Mass Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Ht = Height; PCDAI = Paediatric Crohn's Disease Activity Index; PUCAI = Paediatric Ulcerative Colitis Activity Index; Wt = Weight.

Table 1