

RECENT ADVANCES

Inflammatory bowel disease

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Abstract

The epidemiology, aetiology, clinical features, diagnosis, and treatment of Crohn's disease and ulcerative colitis in children are reviewed, and areas for further research identified.

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This article focuses on Crohn's disease (CD) and ulcerative colitis (UC) in children. It should be remembered, however, that there are less common causes of colitis in infants and young children, such as food allergy.¹

Epidemiology

Recent studies from Wales² and Scotland³ have suggested that there has been an increase in paediatric inflammatory bowel disease (IBD) in the 1980s and 90s, with the incidence of CD being at least twice that of UC. There is still debate as to whether this is a true increase (or an increase in pick up rate) and it is not clear whether or not this increase in incidence has now reached a plateau.⁴

The British Paediatric Surveillance Unit (BPSU) has recently finished a study of IBD in the UK⁵; results suggest an estimated incidence of 5.3 per 100 000 children under the age of 16, equivalent to approximately 700 new cases per annum in the UK and Republic of Ireland, with CD being at least twice as common as UC. The mean age at diagnosis was 11.8 years (median 12.6 years), 13% of cases developing in children aged less than 10. Although there was a median delay period from the onset of symptoms to diagnosis of five months, 25% of children apparently had suffered symptoms for more than one year prior to diagnosis. The length of delay varied significantly between regions and in some a prolonged diagnostic process appeared to be a significant factor in the delay. This may have implications for the overall care of children needing investigation and treatment of potential IBD in the UK as a whole over the next decade.

Aetiology/pathophysiology

Despite a large amount of research, there is still little clear understanding of the causation of CD or UC, or indeed whether or not there may be a common pathophysiological cause.⁶

There is no doubt that there is a genetic preponderance for both diseases and epidemiological data are most consistent with the idea that CD and UC are related polygenic diseases.⁷ Gene linkage studies have been undertaken to try to determine the identity and number of possible susceptibility genes⁸; known HLA correlations are HLA DR3 and DQ2 in determining the extent of the disease and HLA DR103 in predicting severity. Susceptibility genes for IBD also appear to be located on chromosomes 3, 7, and 12, with CD specifically on chromosome 16 and UC on chromosomes 2 and 6.⁸ However, not all the gene locations have been replicated in different populations and further genetic studies are pending.

It is clear that there is also an environmental factor or factors necessary to trigger and maintain the diseases. Specific genes may well interact with environmental factors, which may include bacterial pathogens or their products, dietary components, childhood infections, as well as a host of other possibilities.⁶ The basic problem appears to be an over stimulation/over reaction of the mucosal immune system to a particular antigenic stimulus in genetically susceptible individuals, and it is likely that the antigenic stimulus (organism, food antigen, etc) may vary from case to case. Inflammatory cytokines (interleukin 1, tumour necrosis factor α (TNF α)) tend to be raised consistently in IBD mucosae and TNF α has been the target of possible new therapeutic agents in blocking its activity in a novel form of therapy for CD.

Although there has been controversy over the measles, mumps, and rubella vaccine, there is little credible evidence that this is related to the development of IBD and, at present, the overwhelming proof is that there is no link between the two.

Clinical features/complications

The recent BPSU study suggests that 10% of patients may be of Asian origin (an over representation compared with the overall population) with some 5% of patients being of Afro-Caribbean origin.⁹ There is a slight male preponderance (58%) and most of the recent studies have suggested that in CD, one third of patients have small intestinal disease, one third ileocolitis, and one third colitis, with total colitis being more common (50%) than segmental colitis or isolated proctitis.

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A variety of extraintestinal manifestations of IBD continue to be described, including orofacial granulomatosis; the frequency and importance of growth failure as a primary manifestation of CD should be stressed.¹⁰ Poor linear growth may be the first obvious manifestation which must be monitored carefully as there is evidence that this can be successfully reversed by prompt treatment.^{11 12} Equally, it is important that there is careful follow up of growth and pubertal development of children with IBD, preferably in a joint paediatric IBD/growth clinic, where specific expertise can be shared.

Osteopenia has recently been recognised as an important complication of IBD, particularly in children with CD; although the mechanisms are not yet fully elucidated, the cause appears to be a combination of both the disease itself and drug treatment with steroids.^{13 14}

Diagnosis

Blood sampling may give an important clue as to the diagnosis, and there may be abnormalities of the full blood count (particularly a high platelet count, anaemia, and neutrophil leucocytosis), as well as raised inflammatory markers such as C reactive protein and erythrocyte sedimentation rate. However, if the clinical suspicion is high, further more specific diagnostic tests should be undertaken.

Radiological investigations remain important, with barium contrast studies being particularly useful in the investigation of the small intestine. Endoscopy remains the most important tool and colonoscopy has superseded the barium enema as the primary investigation of the lower bowel. Current opinion suggests that an upper intestinal endoscopy should be performed at the same time as a colonoscopy, as a majority of patients with IBD may show histological abnormalities in the upper gastrointestinal tract, which may be useful in diagnosis.¹⁵

White cell scanning has been proposed as a useful investigation for initial screening/follow up,¹⁶ but there is continued debate about how sensitive and specific this investigation may be. The newer tools of ultrasound, computed tomography scanning, and magnetic resonance imaging are still under evaluation, and not yet part of routine practice.

Treatment

The treatment options for CD and UC have become more varied over the past decade with the increasing use, by paediatric gastroenterologists, of enteral nutrition as the primary therapy to induce remission. The alternative and time tested approach of using drugs such as steroids and acetylsalicylic acid (ASA) derivatives is still common; there have been advances in the use of immunomodulatory drugs (such as azathioprine and mercaptopurine) and the advent of new "biological drugs" such as anti-TNF α monoclonal antibody.

STANDARD DRUG THERAPY

Standard therapy is corticosteroids plus ASA derivatives, particularly for terminal ileal and

colonic disease. Immunomodulatory drugs, such as azathioprine and 6-mercaptopurine, which may allow reduction or cessation of steroids and also help to maintain remission, are being increasingly used.^{17 18}

Newer therapeutic agents such as anti-TNF α antibody, budesonide, and thalidomide are yet to be fully evaluated in paediatric practice; these should be restricted to paediatric gastroenterology centres.

NUTRITIONAL THERAPY

A major advance is that enteral nutrition is now used as primary therapy for active CD by the majority of paediatric gastroenterologists in the UK. However, this practice still remains relatively rare in the USA and among colleagues who treat adults.¹⁹

An analysis of five randomised clinical trials, comprising 147 children, showed that enteral nutrition was as effective as corticosteroids in inducing remission.²⁰ However, there is still debate throughout the world as to the appropriate place for enteral therapy in the treatment of CD, and randomised trials involving large numbers of patients are required. Several questions remain unanswered: how the enteral therapy works (whether a polymeric diet is as effective as an elemental diet); whether or not large intestinal disease is treated as effectively as small intestinal disease; and the role of ongoing maintenance—there is some evidence that intermittent periods of enteral feeding may maintain remission,²¹ but these results need to be confirmed.

SURGERY

Well timed surgical intervention also remains very important, both in the acute and chronic situation. It is particularly valuable in children with specific growth problems who are nearing puberty and is indicated when there is a failure of other treatments to induce adequate remission. It is very important as an option when the disease is not too extensive and it is feasible to resect the affected bowel.¹² The early use of surgery can be vital during the narrow window of therapeutic opportunity before the pubertal growth spurt is complete.

Colectomy in UC is curative but in CD, although surgery may modify the immediate outcome, it does not appear to prevent recurrence.²²

The future

The psychosocial aspect and quality of life issues are being investigated as some follow up studies of children with IBD from Scotland have suggested that young adults may continue to have problems with self esteem and employment. This is an important area for further study. Furthermore, it is very important that there is a paediatric adolescent IBD handover clinic available in major centres, to minimise the sometimes difficult transition from paediatric clinic to adult gastroenterology clinic.

The issue of who cares for children with IBD continues to be debated. For a variety of reasons it is clear that all such children should

be seen at some stage by a paediatric gastroenterologist, but that ongoing shared care with a local paediatrician/adult gastroenterologist may be acceptable in some areas, depending on distance travelled and local expertise. It is important for each region to carefully define such pathways of care; there must be provision of adequate numbers of paediatric gastroenterologists to ensure that all children have access to specific expertise.

An important advance is the formation of an IBD working group responsible to the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition (BSPGHAN). Encouragingly, the BSPGHAN has identified IBD as a priority by establishing the National Paediatric IBD Register which is ongoing and will be very important for cohort follow up of patients. Secondly, the BPSU epidemiological survey is the first prospective national survey of IBD in childhood,^{5,9} the full results of which will soon be published; it will be very useful to repeat this in five years time in order to determine whether the incidence is increasing or not. Thirdly, it is vital that specialised centres in the UK (and Europe) coordinate their research efforts to answer many of the questions that still remain, particularly regarding the appropriate treatment for childhood IBD; this is the responsibility of the newly formed IBD working group within BSPGHAN. We still have a lot to learn but the mechanisms are now in place for there to be UK coordination of such research.

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