Annotations

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is a paediatric blind spot. Most paediatricians consider it a disorder that falls under the remit of geneticists, surgeons, or gastroenterologists but all should be aware of the condition. FAP is characterised by the development of adenomatous polyps in the colorectum, in some cases numbering in excess of a thousand. In a known family, even a single polyp is virtually diagnostic, though such a polyp must be histologically distinguished from a juvenile polyp. The birth prevalence of FAP is about one in 8000[1] and over half develop polyps under the age of 16. Screening usually starts around puberty, although rarely malignancy can develop as young as 5 or 6 years.[2–4] Extra colonic tumour both benign and malignant can also occur – that is, hepatoblastoma, intracranial tumours, benign cystic osteomas of the jaw,[5] desmoid tumours, and multiple sebaceous cysts. The presence of these features in the past attracted the diagnostic label of Gardner's syndrome. Recent molecular genetic studies, however, have confirmed the clinical suspicion that Gardner's syndrome and FAP are the same condition.

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) was first described in individuals with Gardner's syndrome.[6] Subsequent analysis showed that the majority of gene carriers could be distinguished from the normal population by the presence of these benign retinal pigment defects.[7] The presence of five or more such lesions on indirect fundoscopy may be regarded as diagnostic particularly if they include large lesions.[8]

Genetics

FAP is autosomal dominant and results from loss of function of the *APC* gene on chromosome 5.[9] This discovery in 1991 transformed the diagnosis and instead of offering a 50/50 risk of developing the disease and, therefore, early colonic cancer, it became possible to identify children on the basis of the defective gene. The *APC* gene comprises 15 exons with a 9 kilobase RNA transcript.[10] In total, the different mutations number in the hundreds. As with most genes, the size of the transcript is such that sequencing for mutations is a slow and laborious process. The newer techniques of exon scanning allow a significant proportion, and in the near future the great majority, of mutations to be identified by in various ways exploiting the abnormal molecular structure associated with the mutation.[11] One particular mutation, the 5 base pair deletion at position 1309, accounts for 10% of cases and appears to be associated with a greater likelihood of paediatric presentation.[12]

Powerful techniques raise ethical issues not least because it becomes possible to identify an adult onset disease in infancy or even before birth. Most families state that they would prefer to know as soon as possible whether a child is affected. A recent working party report of the Clinical Genetics Society, however, has emphasised the benefits of avoiding presymptomatic diagnosis in childhood unless there are strong clinical arguments in its favour. FAP is generally regarded as an exception as early screening must begin in adolescence because of the risk of carcinoma.

Screening

FAP is the paradigm for targeted screening; relatives have clinical evaluation including indirect fundoscopy for CHRPE and molecular genetic analysis to determine carrier status. Carriers require at least annual flexible or rigid sigmoidoscopy while others prefer colonoscopy. In most cases, children at risk are introduced to bowel examination in an adult endoscopy unit by the surgeon or gastroenterologist responsible for the family. In the Northern region, however, a genetic register is maintained by a genetic nurse directed by a consultant surgeon and clinical geneticist.

After consultation with adult surgical units it was agreed that all children should undergo endoscopy in the paediatric gastroenterology unit. This has helped to ensure that early screening experiences are seen in a positive light as the subsequent annual examination is dependent upon voluntary participation. Almost all of Britain now has a regional polyposis register, most based on the regional genetics services though a notable exception is, of course, the world's first polyposis register which was established at St Mark's Hospital in London, the specialist centre for colonic surgery. Projects are currently underway in London and Newcastle to assess the psychological effects of genetic screening. Paediatric endoscopists can play a central part in such studies.

Treatment

The potential for involvement of paediatricians could increase significantly if, as is hoped, we are able to move towards effective non-surgical therapeutic strategies. At present, the usual practice is to refer adolescents or young adults for resection of the colon with ileorectal anastomosis as soon as polyposis is established. It is reasonable to delay surgery to the end of the teens if polyps are small and not dysplastic but delay further into adulthood carries a growing risk of interval cancer regardless of screening frequency and polyp removal.

The polyposis gene is relatively large but it is theoretically possible that the gene could be introduced into a vector such as an adenovirus and delivered to the colonic wall so as to slow or prevent the progression to malignancy; research strategies directed towards this goal are now being developed.

Such developments are relevant in public health terms for while FAP contributes less than 1% to total colonic cancer deaths the *APC* gene is thought to be initiative in a majority of colonic tumours as a result of somatic mutation.[13] Any measures that can have an impact on this genetic change in carriers of FAP might ultimately become generally applicable to the older population. Can we all look forward to taking our colonic release capsule with the

APC gene in a modified viral vector to ensure the colonic epithelium behaves itself?

The CAPP study

Therapeutic measures tailored to the genetically susceptible child with FAP have now begun to be tested. In 1993 the European Community funded the CAPP study (Concerted Action on Polyposis Prevention) coordinated by JB from Newcastle. This links together 30 European polyposis registers in order to identify individuals from 10 years onwards who carry the polyposis gene and have an intact colon. This cohort of young gene carriers will test, by double blind randomised trial, two treatments that may slow progression of the disease. Enrollees will take a daily supplement of resistant starch, with digestible starch as control, or a low dose of aspirin or placebo.[14] The choice of these two interventions is based on recent epidemiological and experimental data.

Resistant starch

There is a strong negative correlation between the intake of starch in national diets and the incidence of colonic cancer. The correlation between cancer incidence and population starch intake is much closer than with fibre intake.[15] Like fibre, starch can have an impact on transit time but there are also grounds for believing that it can have a much more significant biological effect. A substantial proportion of the starch in several dietary constituents takes the form of 'resistant' starch. This term refers to its resistance to digestion by alpha amylase in the upper intestine.[16] This may be due to the 'packaging' of the starch in seeds, etc, or because the starch is crystalline such that the amylase enzyme cannot gain access. When heated, resistant starch will almost always become gelatinised and digestible, though on cooling it is liable to recrystallise and again become resistant to digestion. The modern Western diet in most cases is very low in resistant starch.

If starch reaches the colon, it is digested by commensal bacteria to short chain fatty acids and of these it is probable that butyrate is the most important as it is used by the colonocyte almost entirely as an energy source. Studies in vitro have shown that butyrate causes colonic cells to differentiate. The attraction of starch as an intervention is that it can be studied by a controlled trial using wheat starch as a digestible placebo alternative. In everyday diets, the most palatable form of resistant starch is the banana; 40% of the starch is in resistant form before the banana is fully ripe. Needless to say, use of the banana would present practical problems in terms of placebo control. Instead, the dietary supplement will be 30 g of white powdered starch (about a tablespoonful) which will be half potato starch and half hylon 7. The latter is a maize which, owing to a mutation in its genetic make up, was found to produce starch which was entirely resistant to amylase digestion. This mixture should deliver a relatively even load of resistant starch to the whole colon. The starch supplement is offered as flavoured drinks and as a powder to be mixed with any cold foodstuff. Gene carriers will be expected to take the daily supplement for as long as possible up to a maximum of five years depending on the timing of their surgery, which should not be altered because of their participation in the trial. The placebo group will receive indistinguishable gluten-free wheat starch which is fully digestible in the upper gastrointestinal tract.

Aspirin

Aspirin was added to the trial after the recent recognition that regular users in epidemiological studies are at significantly reduced risk of colonic cancer. For example, Thun *et al* found that the relative risk of colonic cancer was 0·6 in those taking 16 or more aspirin per month and this was considered a significant departure from normal.[17] In itself, this is relatively weak evidence as the use of aspirin may simply indicate other lifestyle factors which affect the incidence of colonic cancer or, indeed, the common gastrointestinal side effects may simply have increased the rate of early diagnosis. Against this, is the evidence that the related antiprostaglandin sulindac, which achieves a more active form in the colon, can be used in patients to bring about polyp disappearance in a significant proportion of individuals.[18] Furthermore, studies of patients with rheumatoid arthritis who use antiprostaglandins on a large scale have shown a reduced incidence of colonic cancer in this group also.[19] The basis for the effect of antiprostaglandins remains obscure but the availability of aspirin for low dose studies makes it an attractive option for the CAPP study. In order to maximise the statistical power the aim will be to identify up to 400 gene carriers and randomise these to both treatments in a factorial design. End points will rely upon regular video endoscopy. Independent observers will assess whether the rectum is visually better, worse or the same and, in addition, biopsies will be collected to permit crypt cell proliferation analysis.

Canaries not guinea pigs!

Starch and aspirin are attractive treatments as they are relatively benign. If either or both treatments could be shown to slow the progression of polyp formation and ultimately to delay the need for intervention surgically, it would then be justified to consider much larger scale population studies in the older generations to see whether the current annual British death rate of 20 000 people from colonic cancer might be reduced. The young people who carry polyposis are highly motivated to try out these interventions for the sake of themselves and their families. They will also achieve a major advance in the treatment of colonic cancer in the general population. In coal mining areas, rescue teams still carry canaries with them because their greater sensitivity to gas means that they can warn the miners of impending danger. Those who inherit one defective allele at the *APC* locus are like canaries for the general population; their genetic constitution gives them an unwelcome head start in susceptibility to the environmental influences which lead to cancer. We may anticipate other such examples where preventive studies in paediatric patients with rare genetic disorders will be an attractive first step towards the development of population strategies for the prevention of late onset disease.

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Autologous transfusion and reducing allogeneic blood exposure

Autologous transfusion in childhood

Allogeneic blood will continue to be the only form of replacement therapy available to the vast majority of patients requiring blood transfusion. Although the blood supply has never been safer in countries such as the UK, many clinicians now question the need for transfusion of patients with moderately low concentrations of haemoglobin as there is no evidence that mild anaemia will contribute to perioperative morbidity.[1] Some will consider autologous transfusion or other alternatives to donor blood. Autologous blood transfusion is not a new idea but has been little used in children in the UK as opposed to some centres in the USA where it has been widely used, often eliminating the need for allogeneic blood transfusion. There are three methods of autologous transfusion that can be used singly or in combination: (i) predeposit, (ii) acute normovolaemic haemodilution, and (iii) intraoperative or postoperative red cell salvage. Whether there is a good case for any of these procedures before or during paediatric elective surgery is debatable. The advantages are that infection cannot be transmitted from donor to patient, that alloimmunisation is completely avoided, and that there is no risk of immune modulation by transfusion. The disadvantages are largely practical and include limited availability of small blood collection sets and salvage equipment, the necessity for good venous access, and cooperative patients. Also, facilities or expertise for the collection of autologous blood or for normovolaemic haemodilution in children are not always available and the cost of predeposit autologous donation exceeds that of blood from the national blood supply.[2]

Potential benefits of minimising allogeneic transfusion

Awareness of the risk of transfusion transmitted disease has heightened with the advent of HIV and this is usually the underlying reason for a request for autologous blood transfusion. Every effort is made by the National Blood Transfusion Service (NBTS) to minimise the risk of harm arising from transfusion. All blood and plasma donations are screened for antibodies to HIV-1 and HIV-2, hepatitis C, syphilis, and hepatitis B surface antigen. Additionally, selection criteria are applied to exclude donors who admit to activities which render them at higher risk of having infections transmissible by blood transfusion.[3]

The 'window period' between a viral infection and detectable seroconversion does, however, allow a donation taken during the early phase of infection to remain undetected. Donated red blood cells and platelets cannot, at present, undergo viral inactivation and remain viable. There is, therefore, a real but very small risk of viral transmission; for HIV, this has been estimated in the UK as approximately one in 3 000 000 units transfused. The risk of post-transfusion hepatitis B has been calculated as approximately one in 20 000 and, with the recognition and screening for antibodies to hepatitis C, the risk of hepatitis C virus transmission has decreased to less than one in 13 000 units transfused (J A Barbara, M Contreras; personal observations).

Transfusions of donor blood may stimulate the formation of alloantibodies against red cell, platelet, white cell, or plasma protein antigens.[4] Although this is undesirable at any age, it is particularly unwelcome in children who may encounter subsequent difficulties in relation to pregnancies or further transfusion. Transfusion related acute lung injury (TRALI) is a rare complication of transfusion in which donor antileucocyte antibodies cause severe pulmonary damage in a transfusion recipient.[5] Use of autologous blood avoids all these complications.

Some reports have suggested that the rate of postoperative bacterial infection distant from the site of operation is lower in recipients of autologous blood than in patients who have received allogeneic blood.[6–8] Most of these studies are small and further evidence is required before this can be regarded as proved.

Alternatives to allogeneic blood transfusion

(A) REDEFINING THE 'TRANSFUSION TRIGGER'

Surgeons and anaesthetists should consider whether it is justifiable to routinely return the packed cell volume to preoperative values when it is known that a packed cell volume of 25–30% decreases blood viscosity and maintains adequate tissue oxygenation as long as the blood volume remains normal. Several eloquent examples of the very low packed cell volume values that can be tolerated by children have been published.[9–11] On the other hand, in newborn infants undergoing surgery, a higher packed cell volume is desirable because of their predominantly fetal haemoglobin.

Hypotensive anaesthesia, in expert hands, is well tolerated in children who have no problems of coronary artery perfusion; it can prevent the need for transfusion of allogeneic blood.[12]