Overview of screening and management of familial adenomatous polyposis

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Abstract
The rarity of familial adenomatous polyposis (FAP) means that many clinicians may be unaware of the major advances that have taken place in screening for the condition over the past five years. This review is not only to document the current scene but also to give details of those involved in establishing registries throughout the country. FAP is a hereditary disorder which carries with it almost a 100% risk of colorectal cancer. The aim of screening is to detect gene carriers before they present with symptoms attributable to colonic polyps. In this way the incidence of colorectal cancer can be greatly reduced. The use of gene probes to identify patients with FAP is in its infancy but in selected pedigrees gene carriers can be identified using a venous blood sample. The recognition that congenital hypertrophy of the retinal pigment epithelium is an extracolonic manifestation of FAP in most pedigrees allows non-invasive ophthalmological screening of relatives at risk. The combination of these new screening methods with an effective regional registry for FAP can increase the number of patients detected by screening rather than by symptoms. This facilitates appropriate prophylactic surgery and reduces mortality related to colorectal cancer.

The rarity of familial adenomatous polyposis (FAP) means that many clinicians may be unaware of the major advances that have taken place in screening for the condition over the past five years. This review is not only to document the current scene but also to give details of those involved in establishing registries throughout the United Kingdom.

FAP is a rare hereditary disease characterised by the development of large numbers of adenomatous polyps (more than 100) in the colon and rectum, which in the absence of surgical intervention invariably progress to adenocarcinoma. Until recently, identification of patients with FAP before they presented with clinical symptoms was largely dependent on sigmoidoscopic examination. Advances in the knowledge of the genetic defect of FAP has allowed identification of probable gene carriers. Accurate and helpful genetic counselling may thus be offered in the childbearing years. Written against the background of these recent developments, this review provides simple guidelines for clinicians involved in the management of such families.

For most doctors the general area of colonic polyps has become confused. The main distinctions which have helped our understanding have been based on histopathology, while the description of eponymous syndromes has confused rather than clarified the issues. An important historical landmark in our understanding of colonic polyps came from Woodward’s distinction between neoplastic and inflammatory lesions in 1881 which was followed a year later by an account of a brother and sister who both had multiple adenomatous polyps in the rectum. As more elaborate pedigrees appeared the genetic nature of FAP was recognised and screening of relatives at risk by sigmoidoscopic examination followed shortly. The inheritance pattern of FAP was established as mendelian dominant without sex linkage.

The risk of malignancy in FAP was first noticed in 1887, but it was not until 1925 that Lockhart-Mummery postulated the adenoma-carcinoma sequence. By the 1940s surgical removal of the colon was a sufficiently safe procedure to offer prophylaxis against the risk of colorectal carcinoma in FAP patients. For the next 40 years colectomy remained a generally accepted procedure, but the last 10 years have seen two major developments – more effective screening for the disease and the increasing acceptance of panproctocolectomy with construction of an ileal reservoir.

Gardner’s syndrome is probably the best recognised eponymous condition linking colonic polyps with extracolonic manifestations of multiple epidermoid cysts, osteomas, and desmoid tumours. Similar expression of these features in FAP has led to the suggestion that the two syndromes are identical. Gene mapping of both conditions to chromosome 5q supports this view. The association of tumours of the central nervous system with FAP (Turcot’s syndrome) and an association with endocrine neoplasia are also probably different expressions of the same genetic defect.

Screening programme for FAP
Some degree of scepticism has been expressed about the value of screening programmes, which in some instances identify the affected relatives with little opportunity to treat the detected disease. This is in striking contrast to FAP in which the risk of large bowel malignancy in affected relatives approaches 100%. The traditional practice of contacting several first degree relatives to carry out sigmoidoscopy may fail to identify many potential carriers in an extended family tree (Fig 1). This immediately raises the question of who should conduct the search for other affected relatives, and a team approach involving the surgeon, a geneticist, and usually a genetic nurse is essential.
Figure 1: Establishing the full extent of a family with familial adenomatous polyposis may be difficult. Traditionally this has been undertaken by the surgeon. The pedigree (from the Northern Regional Registry) shows the potential shortcomings of this approach. Affected members of the family are shown in black, men as squares and women as circles. Family members who are dead are denoted by an oblique line through their symbol.

The justification for screening programmes to identify presymptomatic patients comes from figures showing a much higher incidence of colonic carcinoma in patients who present with symptoms. The Japanese Polyposis Register published their data in 1977 showing a 57% incidence of malignancy in symptomatic patients compared with 33% in asymptomatic patients. These figures are disappointing. However Jarvinen et al in Finland found that only three of 50 patients identified by screening had a carcinoma compared with 54 of 87 symptomatic patients. The most recent figures from the Northern Region Health Authority in England showed no malignancies in 25 patients detected through screening compared with 10 in 31 patients who presented with symptoms. The current aim of screening is to identify patients carrying the abnormal gene before the appearance of rectal polyps.

Impact of congenital hypertrophy of the retinal pigment epithelium, DNA probes, and age of onset curves on screening

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) was first described in an FAP patient in 1935, although the significance of 'several punctate pigmented areas in the fundi' (Fig 2) was not recognised at the time. Blair and Trempe were the first to realise that the condition was an extracolonic manifestation of Gardner's syndrome and more recent studies have shown the sign to be present in most patients with FAP. Its importance in screening for FAP lies in the fact that it is present from birth and it can be identified non-invasively by indirect ophthalmoscopy. This is in contrast to polyps, which develop later and can only be detected by sigmoidoscopy. Lesions are present in at least 80% of gene carriers and the most recent work from the Northern Region suggests...
that the presence of four or more lesions gives a sensitivity of 87.8% and a specificity of 100% in 48 unrelated pedigrees. Family members are most effectively screened by an ophthalmologist with an interest in this condition. Conventional direct ophthalmoscopy will miss CHRPEs in 70–80% of cases due to their peripheral location.

The gene for FAP has been localised to the long arm of chromosome 5 and has recently been sequenced. It is therefore likely that the use of gene probes in FAP which is currently in its infancy will provide much more useful information. Newer techniques may allow retrospective analysis of paraffin embedded samples when living family members are not available. Four probes (p227, c1p11, y5.48, and acb27) are in common usage and the newer more closely linked polymorphic probes are currently being evaluated. Murday and Slack documented the age of development of polyps in an FAP population (Fig 3). Using this concept of age of onset curves, CHRPEs, and gene markers, probable presymptomatic gene carriers can be identified.

In practice the genetic nurse interviews the patient, drawing up the family tree of all living relatives with details of any known deaths from bowel cancer. Arrangements can then be made for fundoscopy and blood taken for DNA analysis. Endoscopic screening usually starts at the age of 14. An unpleasant screening experience at this age may lose the patient and other family members from follow up, so patients of this age must be handled with great tact. Annual endoscopy by rigid or flexible sigmoidoscope is usually performed until the age of 50. Although not necessary for the examination, it may be helpful to use hypnotics with the anxious patient. In most patients there is a preponderance of polyps in the rectum. This means that colonoscopy is not usually necessary. Occasionally patients may have right sided polyps without rectal evidence of FAP. Two such patients exist in the Northern Region and both were diagnosed by colonoscopy, although routine multiple colonoscopy is not advocated.

It should be emphasised that endoscopy is a diagnostic tool rather than a method of treatment. Endoscopic polypectomy has a bleeding and perforation rate of 0.5–1.2% hence multiple polypectomies in the same patient significantly increase this small risk. Once FAP has been confirmed by the presence of polyps in a young person with a family history of FAP surgical management can be discussed.

**Surgery in FAP**

It was not until the 1930s that elective prophylactic surgery for FAP was introduced and in 1934 Lockhart-Mumery reported four colectomies for the disease. Earlier attempts at surgical treatment were largely confined to local excision of large rectal polyps. Since mortality from perineal excision was greater than 10% in the early part of this century, abdominal surgery was restricted to patients who already had a carcinoma. In 1939 McKenney reported performing either total colectomy with ileostomy or ileosigmoid anastomosis. The first total colectomy and ileorectal anastomosis was carried out at St Mark’s Hospital in 1948 by O V Lloyd-Davies. Until the introduction of proctocolectomy with ileal reservoir in 1976, the mainstay of surgical prophylaxis was colectomy and ileorectal anastomosis, with panproctocolectomy and terminal ileostomy as a more radical alternative.

**Colectomy and ileorectal anastomosis**

Colectomy and ileorectal anastomosis is still the most widely used surgical prophylaxis for FAP; it is a safe procedure with a mortality of less than 1% and a major morbidity rate of about 10%. Disadvantages of the procedure lie in the need for regular sigmoidoscopic examination of the rectum postoperatively with the risk of developing adenocarcinoma in the retained rectum. The incidence of rectal carcinoma is reported between 6% at 20 years and 55% at 30 years. Bussell et al. found that the cumulative risk of rectal carcinoma was 13% in 166 patients treated over 40 years by ileorectal anastomosis. Sarre et al. from the Cleveland Clinic, reported a similar rate of rectal cancer with a crude cancer rate of 6.7% in patients who had had an anastomosis and a 12% incidence of rectal cancer at 20 years. Bulpin reported a 13% incidence of rectal...
cancer after 10 years in 58 patients on the Danish registry, while Watne\textsuperscript{14} found that seven of 32 patients developed rectal cancer at a mean of 14 years after their anastomosis. Jarvinen\textsuperscript{14} found a rectal excision rate of 7.7\% in 52 patients on the Finnish register who had had ileorectal anastomosis; pathology of the rectum showed polyps but no carcinoma in all four cases. The South African results reported by Aitken et al\textsuperscript{39} show a 23\% incidence of carcinoma of the rectum at 15 years. The highest incidence of rectal carcinoma was reported by Bess\textsuperscript{49} from the Mayo Clinic, who found a 55\% incidence at 30 years. A further report in 1987\textsuperscript{40} from the same centre suggested a carcinoma rate of 32\% at 15 years, but both these series excluded patients who did not have rectal polyps before primary surgery. Inclusion of all ileorectal anastomosis patients would further reduce the incidence of rectal carcinoma in the Mayo series to 26\% at 15 years.

Colectomy and ileorectal anastomosis has been performed on 20 patients in the Northern Region. Sigmoidoscopic follow up has been undertaken six monthly or annually to treat recurrent rectal adenomas. By January 1989 six patients had needed further surgery to excise the rectum; proctectomy was performed between six and 18 years after ileorectal anastomosis (mean 11.2 years). All of the rectal stumps contained multiple adenomas but no invasive carcinomas. The remaining 14 patients had their surgery one to 19 years ago (mean 10.3 years). The rate of subsequent rectal excision (30\%) is somewhat higher than those reported above.\textsuperscript{34,35}

Variation in the incidence of rectal carcinoma between centres may be explained by two variables. The frequency of follow up after surgery varies between series; patients who miss their sigmoidoscopic examination for two or three years and then present with rectal carcinoma might have been treated before the development of invasive malignancy had they been seen regularly. A second variable is the length of the rectal stump; longer stumps are more difficult to examine adequately and may be more likely to develop malignancy. Ileo-sigmoid anastomosis has been performed in an attempt to decrease postoperative diarrhoea, but the incidence of subsequent carcinoma is higher due to the difficulty of surveillance.

Panproctocolectomy

Although panproctocolectomy is not widely reported as a primary treatment for FAP, it is still the most frequently performed operation for FAP in many areas including the Northern Region Health Authority in England. The first use of panproctocolectomy as prophylaxis in FAP was reported by Miller and Sweet in 1937.\textsuperscript{41} Bulow\textsuperscript{42} found it to be the commonest operation among patients on the Danish register. In 1987 66 of 138 FAP patients had undergone panproctocolectomy, 13 of whom had rectal cancer at the time of surgery. A similar number of patients (52/135) on the Swedish register have also been treated by panproctocolectomy,\textsuperscript{35} whereas only 28 of 216 patients treated at St Mark’s between 1948 and 1984 were managed in this way. In January 1989, 56 of the 59 FAP patients in the Northern Region of England had undergone surgery and 22 of these (average age 34-1 years) had been treated by panproctocolectomy and terminal ileostomy.

Restorative proctocolectomy

Restorative proctocolectomy with ileal reservoir was first performed by Sir Allan Parks in 1976\textsuperscript{43} and has subsequently been used predominantly in the treatment of ulcerative colitis. Of 119 such operations performed at St Mark’s between 1976 and 1986, 37 were on patients with FAP. Provisional results from two groups suggest that an ileal pouch may be the operation of choice for FAP patients\textsuperscript{44,45}; the first large series on patients with FAP was reported by Dozois et al in 1989.\textsuperscript{46} A total of 852 patients have been given ileal pouches at the Mayo Clinic, 94 of whom had FAP. The mortality was zero with operative complication rates of 26\% in FAP patients and 29\% in patients with colitis. Pouch function was better in patients with FAP who had a lower daytime stool frequency, less nocturnal faecal spotting, and less pouschitis.

The ileal pouch-anal anastomosis may form an attractive alternative to ileorectal anastomosis, particularly in young patients with rectal cancer or multiple rectal adenomas at the time of surgery. The longterm results of such surgery, particularly recurrence of adenoma in the pouch, ‘pouchitis’, and faecal continence are not yet available. It may be that the longterm functional results and adenoma recurrence are similar to those after ileorectal anastomosis. It will be at least 15 years before this information is available. In the interim the patient’s preference has an important part to play in deciding between an ileorectal anastomosis and ileoanal pouch.

Complications of surgery

In the Northern Region of England there have been no perioperative deaths but some postoperative morbidity occurred in 18 of 56 patients (32\%). Overall there were 24 complications in 11 of the 22 panproctocolectomy patients, a rate of 50\%. Ten patients needed their ileostomy refashioned, six needed a second laparotomy for small bowel obstruction and four had chronic problems with perineal infection and sinuses. While panproctocolectomy seems to be an attractive option since a single operation eradicates any risk of further rectal or colonic adenomas, there is increasing awareness that FAP is not purely a colonic disease\textsuperscript{47,48}. The disadvantages of a perineal wound, abdominal stoma, potential bladder and sexual dysfunction are disincentives to the use of panproctocolectomy as prophylaxis in FAP. It is still frequently used in patients who present with rectal carcinoma and require excision of the rectum as an essential part of their polyposis surgery. In contrast just three complications occurred in three IRA patients (rate 15\%) and five complications in three pouch patients (rate 37-5\%). The lower complication rate experienced after colectomy and IRA must be balanced against a 30\% chance of requiring rectal excision within 10 years.
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Polyposis registries (Table)

Coordination of an effective regional screening programme is greatly facilitated by establishing a registry for FAP. The aims of a registry are to document all cases of FAP, establish the incidence and prevalence of the disease, and act as a forum for evaluation and discussion of new developments in screening and treatment of patients.

The idea of a polyposis register is not new. The St Mark's Hospital Registry was founded in 1925 and contains 350 families from all over the United Kingdom. There are currently 300 FAP patients from 100 pedigrees under routine medical review at St Mark's, but in spite of attempts to set up a national registry, only two of the 43 FAP families identified in the Northern Region during the past two years were registered at St Mark's. Geographical separation makes it virtually impossible to establish a comprehensive national clinic for FAP impractical.

Similar large registries of patients with FAP exist at the Cleveland and Mayo Clinics. Both consist of patients from all over the United States. Other population based registries exist in Denmark, Finland, and Japan. The Japanese register seems to suffer from many of the same problems as the St Mark's register in that comprehensive coverage of 100 million people in a country nearly 1000 miles long is impractical for one centre. The advantages of concentrating on a small population within a defined catchment area are threefold. Firstly, patient compliance is higher when the screening centre is within easy access of the homes. Secondly, direct contact with the patients is possible for a single member of staff who can build a relationship with the various families. Because of these two factors a more comprehensive coverage of the chosen area allows a clear picture of the prevalence and incidence of FAP to be obtained.

During the first two years of the Northern Region Registry the number of relatives at risk screened for FAP has increased more than tenfold and led to the diagnosis of five new FAP patients. Both DNA analysis and screening for CHRPE have been made available to the whole region and this has helped to identify 23 possible gene carriers. Large bowel examination will lead to the confirmation of FAP in this group of patients within the next few years. It is hoped that this increased screening will lead to smaller numbers of patients presenting with symptoms. If this is the case then the age of diagnosis for FAP will fall. This will lead to earlier prophylactic surgery which is more likely to be 'simpler' and less likely to take place after large bowel carcinoma develops.

Extracolonic manifestations of FAP

There is increasing recognition that the colonic disease may be associated with other clinical features which give some indication of the pleiotropic expression of the genetic defect. Few of the extracolonic manifestations of FAP cause management problems, so prominence is given to those causing some degree of clinical uncertainty.

DUODENAL AND GASTRIC ADENOMAS

Carcinoma of the upper gastrointestinal tract is the commonest fatal malignancy in patients who have undergone prophylactic colectomy. The adenomatous precursors in the stomach and duodenum develop long the colonic polypos and in the study of Jagelman et al occurred a median of 22 years after colectomy.

Gastric polyps are found in up to 60% of patients with FAP, although most of them are hyperplastic foveolar glands and require no treatment. A smaller percentage of patients (2-12%) have true adenomas which are usually located in the antrum. Duodenal adenomas are more common than gastric adenomas (33-88%) and are clustered around the ampulla of Vater. Adenomas in both stomach and duodenum exhibit the same premalignant potential as colonic adenomatous polypos.

Screening FAP patients for upper gastrointestinal adenomas has been advocated, although their management is unclear. Clinical difficulty occurs because size is no guide to the malignant potential; adenomatous changes can occur in the large flat mucosa and biopsy of a single lesion is likely to miss malignant change in up to 50% of cases. Treatment options at both sites include snaring, diathermy, laser, local excision, and radical resection. Many of the polyps are sessile and are thus not suitable for snaring; laser or diathermy may be limited in the duodenum due to the proximity to the ampulla. Furthermore, the high rate of false negative biopsies may give the clinician an unwarranted sense of security in patients who may require a curative resection. Local resection can be limited by anatomical considerations and even benign tumours can have a high recurrence rate. Radical surgery either by gastrectomy or pancreaticoduodenectomy is the treatment of choice for non-metastatic invasive tumours but has also been advocated for benign lesions because of their high recurrence rate after conservative treatment.

Despite the controversy it seems reasonable to begin screening with upper gastrointestinal endoscopy in patients after their colectomy to establish the natural history of these lesions. It is hoped that by treating early adenomas less radical forms of treatment may be used.

DESmoid TUMOURS

Desmoid tumours are slow growing, locally invasive proliferations of fibroblasts and are well known to be associated with FAP. The lifetime risk is 8% for males and 15% for females, and they occur most commonly in the small bowel mesentery, retroperitoneum, and abdominal wall. Symptoms arise because of the tumour mass and also because of intestinal obstruction. During pregnancy the mass may grow rapidly, while after the menopause they may regress, which suggests some hormonal dependence. Some authors report good results after radical resection, but most have a high recurrence rate and consequently advise that surgical treatment should be confined to biopsy and bypass of symptomatic lesions. Medical treatment with...
tamoxifen, sulindac, and toremifene has shown promising results.

**BONE AND DENTAL ABNORMALITIES**

Ostomas of the mandible, maxilla, and sinuses occur in up to 90% of cases of FAP and these changes may predate polyp development. Some groups have proposed the use of orthopantomograms (mandibular radiology) to aid in pedigree analysis, although others have found difficulty in interpreting the results. The value of orthopantomograms awaits further evaluation. Odontomas, dentigerous cysts, and supernumary teeth are associated with FAP and may predate the development of colonic polyps but rarely present to the general surgeon.

**EPIDERMIC CYSTS**

Epidermoid cysts associated with FAP are often seen in children and may be used as a pointer of gene carrier. Their high prevalence in the normal adult population precludes such use in the older age groups.

**OTHER TUMOURS**

Adrenal, thyroid, carcinoid, and central nervous system tumours have also been reported in FAP but their incidence is very low.

This work was supported with the help and support of the permanent members of the Northern Region Registry. We wish to thank Mr A Gunn, Mrs D P Chapman, and Dr J Burn for their involvement in this review.

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Gut 1992 33: 125-131
doi: 10.1136/gut.33.1.125

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