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REVIEW ARTICLE

The Hereditary Colorectal Polyposis

James Church BSC MBChB M Med Sci, FRACS, FACS; Victor W. Fazio, Professor of Colorectal Surgery and Director David G. Jagelman Inherited Colorectal Cancer Registries, Cleveland Clinic Foundation, Cleveland, Ohio, USA

ABSTRACT

Hereditary gastrointestinal polyposis syndromes are rare, accounting for approximately 1% of all colorectal cancers. They are important, however, because of the insight they provide on the genetic mechanisms underlying colorectal carcinogenesis, and because of their devastating effect on the families affected by them. They are best categorized according to the histology of the polyps. This review will summarize current knowledge of the hereditary gastrointestinal polyposes, and will provide recommendations for treatment and surveillance. The Syndromes: The adenomatous polyposes include familial adenomatous polyposis, the most familiar, commonest, and most well known of the polyposes, and *MYH*-associated polyposis, the most recently described. Familial adenomatous polyposis is caused by a dominantly inherited germline mutation in *APC*, a key tumor suppressor gene. The mutation is expressed primarily as colorectal adenomatous polyposis, with 100% penetrance, and affected patients have a 100% chance of developing cancer. Treatment is by prophylactic colectomy or proctocolectomy, and lifelong surveillance of the rest of the gastrointestinal tract is necessary. Cancers and benign tumors may occur in bones, skin, brain, thyroid, adrenals, liver, and duodenum. *MYH*-associated polyposis is due to recessive inheritance of a mutation in *MYH*, a gene involved in base excision repair. Biallelic *MYH* mutations cause a syndrome of mild adenomatous polyposis, with an increased risk of colorectal cancer and neoplasia in the stomach and duodenum. Colectomy is not automatic but depends on the severity of the colorectal polyposis. The hamartomatous polyposes include Peutz-Jehger's polyposis, juvenile polyposis, and other very rare syndromes such as Cowden's Syndrome, Bannayan-Ruvalcaba-Riley Syndrome and Gorlin's Syndrome. They feature colorectal involvement with hamartomatous polyps, although Peutz-Jehger's polyps are unique in showing smooth muscle infiltration of the lamina propria. Peutz-Jehger's Syndrome primarily affects the upper gastrointestinal tract and is usually recognized by the patients' circumoral and buccal pigmentation. The syndrome is due to a germline mutation in *STK11*, and confers increased risks of colorectal, gastric, small bowel, pancreatic, breast, and gonadal cancer. Juvenile polyposis affects the stomach, small bowel and colorectum. Familial cases of juvenile polyposis are often associated with germline mutations in *SMAD4* or *BMPRIA*, two genes involved in the TGF-ß signal transduction pathway. The multiple polyps usually cause severe symptoms leading to colectomy or proctocolectomy. Cowden's Syndrome is not associated with an increased risk of colorectal cancer, but adenomas may arise among the hamartomas and ganglioneuromas. The genotype of hyperplastic polyposis is unknown, but there is increasing evidence of a high cancer risk associated with multiple colonic hyperplastic polyps. The role of prophylactic colectomy has not been defined. The mixed adenomatous/hamartomatous polyposis syndrome has been described in only a few families, with a link to chromosome 15. *CRAC1* is a candidate gene for this syndrome. Conclusion: multiple colorectal polyps are a clue to the possible presence of an inherited syndrome predisposing patients to colorectal cancer. Diagnosis is based on biopsy of a representative number of polyps, documentation of likely extracolonic manifestations, a careful search of the family, and genetic testing for a germline mutation. Treatment depends on the organs affected, the severity of the polyposis and the nature and severity of symptoms. Lifelong surveillance of all affected family members is recommended.

Key words: Adenomatous Polyposis Coli. Gastrointestinal Neoplasms. Colorectal Neoplasms Neoplastic Syndromes, Hereditary. Polyps.

Correspondence
James Church
Cleveland Clinic Foundation
Desk A-30, 9500 Euclid Ave
44195 Cleveland, Ohio, USA
Phone: 1 216 4449052 Fax: 1 216 4458627
E- mail: churchj@ccf.org

INTRODUCTION

Occasionally, an individual physician will meet a patient with a clearly unusual number of colorectal polyps. Sometimes that patient will have a colorectal cancer as well, and sometimes that patient will have a notable family history of cancer. In such a patient the possibility of a hereditary polyposis syndrome should be entertained. If such a syndrome is present, there are serious implications for the treatment and follow-up of the patient him or herself, and for testing and surveillance of the entire family.

Hereditary gastrointestinal polyposis syndromes are rare, accounting for approximately 1 % of all colorectal cancers. They are important, however, because of their devastating effect on the patients and families affected by them, and because of the insight they provide on the genetic mechanisms underlying colorectal carcinogenesis. They are best categorized according to the histology of the polyps. This review will summarize current knowledge of the hereditary gastrointestinal polyposes, and will provide recommendations for treatment and surveillance.

PRESENTATION

How many polyps are too many? How many polyps does it take to suggest the presence of a hereditary syndrome of polyposis? The answer depends on the histology of the polyps. Isolated hamartomas occur occasionally in adults,[1] while isolated juvenile polyps are the commonest colorectal polyp in children.[2] They do not mean that there is polyposis, not do they require intense surveillance. If a more than one Peutz-Jehger's polyp is found in a patient with either a family history of Peutz-Jehger's syndrome, or circum oral pigmentation however, it is a different matter. The diagnosis is established. In most patients, Peutz-Jehger's syndrome presents with complications of the small intestinal polyps, so that the number of colonic polyps is irrelevant. In juvenile polyposis, more than 5 synchronous colorectal juvenile polyps define polyposis.[3] Hyperplastic polyps are common and the definition of hyperplastic polyposis less certain, but the consensus is that more than 20 colonic hyperplastic polyps constitute polyposis. When the polyps are adenomas the distinction between syndromes may blur. More than 100 synchronous adenomas define classical familial adenomatous polyposis (FAP),[4] but may be associated with biallelic *MYH* mutations indicating *MYH*-associated polyposis (MAP).[5] More than 1,000 synchronous adenomas are almost certainly FAP, while less than 100 could mean either attenuated FAP or MAP. The lower limit of adenomas that defines a hereditary syndrome depends on the family context. In a FAP family, any adenoma, especially in a young patient, suggests that the patient is affected. With no family history, 10 or more synchronous adenomas should arouse suspicion.[6]

THE DIAGNOSIS

When multiple colorectal polyps are seen during colonoscopy, a representative number should be biopsied. If there are less than 15 or so, it is reasonable to attempt to clear the colon to provide a baseline against which to judge the rate and severity of recurrent polyposis. The endoscopic appearance of the polyps usually provides a clue to the likely diagnosis. Hyperplastic polyps are somewhat shapeless folds on the mucosa, often associated with excess mucus and a yellowish or "rust" color. Hamartomas are bright "cherry" red, multilobular, with small polyps on the stalks of larger ones. Adenomas are discrete pink polyps, the smaller ones sessile and the larger ones often pedunculated. Biopsy of the polyps confirms the endoscopic diagnosis.

Before the biopsy report is available, a thorough family history is obtained. This should establish the presence of a dominantly inherited syndrome of cancer predisposition. However 50% of patients with juvenile polyposis and 30% of patients with FAP have no family history, while patients with MAP have recessive inheritance in which the parents are unaffected carriers of the mutations. Once a diagnosis is made, patients and their families are referred to a genetics center or registry for counseling and possible genetic testing. At the same time treatment of the proband is begun.

THE SYNDROMES AND THEIR TREATMENT

ADENOMATOUS POLYPOSES

The adenomatous polyposes include familial adenomatous polyposis, the most familiar, commonest, and most well known of the

polyposes, *MYH*-associated polyposis, the most recently described, and hereditary mixed polyposis, the least frequently reported.

FAP

FAP is caused by an autosomal dominantly inherited germline mutation in *APC*, a key tumor suppressor gene located on chromosome 5q.[7] The mutation is expressed primarily as colorectal adenomatous polyposis, with 100% penetrance, and affected patients have a 100% chance of developing cancer. The mean age at cancer is 39 years, although presymptomatic diagnosis by genetic testing or endoscopic surveillance and prophylactic colectomy reduces the incidence of cancer at the time of presentation from about 60% in patients who present with symptoms to less than 10%.[8] Treatment is by prophylactic colectomy or proctocolectomy, and lifelong surveillance of the rest of the gastrointestinal tract is necessary. Cancers and benign tumors may occur in bones, skin, fibrous tissue, brain, thyroid, adrenals, liver, and duodenum. The association of FAP with epidermoid cysts, osteomata, dental abnormalities and desmoid tumors is known as Gardner's Syndrome while the association of FAP with brain tumors is Turcot's syndrome.[9] The expression of the mutation is at least partly determined by its site on the gene. Mutations at codon 1309 in exon 15G, a mutation "hot spot", are always associated with profuse polyposis.[10] Mutations in exons 3 and 4, the 5' part of the gene, cause attenuated FAP with gastroduodenal polyps but few other extra colonic manifestations.[11] Mutations in the 3' end (downstream) of codon 15 cause increasingly severe desmoid disease and mild or even minimal polyposis.[12] Genotype influences surgery in that patients with codon 1309 mutations should always undergo total proctocolectomy, while those with mutations in exons 3 and 4 usually have colectomy with ileorectal anastomosis.[10] Patients with mutations 3' in exon 15 may have their surgery delayed as long as possible in the interest of postponing desmoid development.

There are 3 main issues confronting patients with FAP and their physicians: the choice of surgery, the stomach and duodenum, and desmoid disease.

Choice of surgery

There are 3 options for the surgical treatment of the large bowel: 1. total proctocolectomy and ileostomy (TPC), 2. total proctocolectomy and ileal pouch-anal anastomosis, (IPAA) 3. colectomy and ileo-rectal anastomosis (IRA). Option one is rarely chosen as a primary surgery, except where the anus must be removed because of cancer, or cannot be reached because of desmoid. Option 2 is chosen for patients with profuse polyposis (>1000 colonic adenomas, or >20 rectal adenomas) as these patients are at high risk for rectal cancer if IRA is performed.[10] While IPAA preserves per anal defecation, bowel function is not normal and when there is a mucosectomy and hand-sewn anastomosis, patients may suffer seepage of mucus and liquid stool.[13] A temporary ileostomy is usually performed. IRA is a good option for patients with mild polyposis (<20 rectal adenomas, < 1000 colonic adenomas). It is a simple operation with good bowel function and no stoma. It can be done laparoscopically which is an advantage especially in children and teenagers.[14] Regardless of which option is chosen, patients must return for routine surveillance of their pouch or rectum, both of which are prone to develop adenomas.[15,16]

The Stomach and Duodenum

Over 90% of FAP patients develop gastric fundic gland (hyperplastic) polyps and duodenal adenomas. About 10% develop gastric adenomas.[17] While gastric cancer is an unusual association of FAP in western countries it is more common and more of a concern in Asia. Recent reports of dysplasia in fundic gland polyps hint at the possibility of malignant transformation. The rate of this must be very low however, and prophylactic gastrectomy is not done. Duodenal and periampullary cancer is much more common in FAP. Although the absolute incidence is still low, it is the second most common cause of death in FAP patients. Duodenal adenomatosis can be defined according to the number, size and histology of the polyps.[18] This Spigelman staging can be used to determine surveillance intervals and, more recently, has been used as an indication for duodenectomy. Stage IV duodenal adenomatosis has a 36% risk of duodenal cancer and should prompt strong consideration of surgery. Stages I, II and III can

be followed endoscopically.[19]

Desmoid Disease

Desmoid disease is an overgrowth of fibrous tissue. It presents as a spectrum of disease, from flat white sheets on the mesentery of the bowel (desmoid reaction) to tumors that occur intra-abdominally (80%), in the abdominal wall (15%) or extra-abdominally (5%). About 12% to 15% of FAP patients develop desmoid tumors while another 15% harbor asymptomatic unsuspected desmoid disease.[20] Most desmoid tumors are noticed after laparotomy. Desmoid tumors vary in their aggression and their response to treatment. Some grow rapidly and are lethal, a few disappear, while most are indolent or undergo cycles of growth and regression.[21] Even without rapid growth desmoids interfere with surgical plans by preventing IPAA.[22] They may cause bowel or ureteric obstruction, or fistula formation. There is no predictably effective treatment for desmoid tumors, although non steroidal anti-inflammatory drugs such as Sulindac, estrogen receptor modulators such as tamoxifen and Raloxifene, and the anti-fibrosis agent pirfenidone have all had some success.[23-26] Chemotherapy is reserved for symptomatic unresponsive tumors, using either methotrexate / vinblastine or adriamycin. Resection of intra-abdominal desmoids is a last resort because of the high morbidity, potential loss of large amounts of small bowel, and high recurrence rates.[27]

MYH-ASSOCIATED POLYPOSIS

MYH-associated polyposis is due to recessive inheritance of a mutation in *MYH*, a gene involved in base excision repair. Biallelic *MYH* mutations cause a syndrome of mild adenomatous polyposis, with an increased risk of colorectal cancer and neoplasia in the stomach and duodenum.[5] Colectomy is not automatic but depends on the severity of the colorectal polyposis. The first reports of MAP were published in 2002, and describe a range of patients from those with as few as 7 adenomas to some with over 400.[28,29] The initial populations tested for MYH mutations were patients diagnosed with either attenuated or classical FAP in whom no germline APC mutation could be found. Approximately 5 to 7% of these groups had bi-allelic MYH mutations.[5] Heterozygous MYH mutations occur in about 1 to 2 % of the general population, and may confer some increased susceptibility to colorectal cancer.[30] However for MAP to exist, two heterozygous carriers have to marry. One quarter of their offspring will be affected. The family history in a recessive trait is weak, with parents unaffected, 25% of siblings affected, and evidence of the syndrome on either side of the family.

There are few guidelines on the management of MAP, but those with >20 adenomas can be treated as if they had FAP and offered colectomy and IRA. Some patients with few adenomas may be managed endoscopically. Surveillance of the stomach and duodenum should be as for FAP.

THE HAMARTOMATOUS POLYPOSES

The hamartomatous polyposes include Peutz-Jehger's polyposis, juvenile polyposis, and other very rare syndromes such as Cowden's Syndrome, Bannayan-Ruvalcaba-Smith Syndrome and Gorlin's Syndrome. They feature colorectal involvement with hamartomatous polyps.

Peutz-Jehger's Syndrome

Peutz-Jehger's Syndrome is a dominantly inherited syndrome of hamartomatous polyposis primarily affecting the upper gastrointestinal tract. Peutz-Jehger's polyps are histologically different to juvenile polyps in showing smooth muscle infiltration of the lamina propria. Affected patients are usually recognized by their circumoral and buccal pigmentation.[31] Peutz-Jehger's syndrome is due to a germline mutation in *STK11*, a gene coding for a serine-threonine kinase. Germline mutations can be found by genetic testing in 70% of clearly familial cases and 30 to 70% of patients with no family history.[32] The mutation confers increased risks of colorectal, gastric, small bowel, pancreatic, breast, and gonadal cancer.[33] Patients typically present in their childhood with small bowel obstruction due to intussusception of a jejunal hamartoma. This leads to surgery in many cases, with resection of the offending polyp and segment of small bowel. Full work-up of symptomatic patients includes colonoscopy, esophago-gastro-duodenoscopy (EGD) and

either small bowel radiology, small bowel endoscopy or capsule endoscopy. Capsule endoscopy provides the most accurate indication of the state of the small bowel. Then surgery can be planned during which intra-operative endoscopy is used to identify and help remove all visible lesions. Polyps that cannot be removed endoscopically are removed surgically through enterotomies. This "clean sweep" approach promises to minimize the need for repeated surgeries that tends to happen when surgery is limited to the section of bowel causing symptoms.[34] The risk of colorectal cancer associated with Peutz-Jehger's syndrome is higher than normal but relatively low compared to the very high relatives risks of gastric, small bowel, and pancreatic cancer (213 x, 520 x and 182 x respectively).[33] The risks of lung, endometrial, breast and germcell tumors of the ovary and testes are all increased compared to the normal population, by a range of 15 to 30 fold. [33]

Juvenile Polyposis

Juvenile polyposis affects the stomach, small bowel and colorectum. About half the cases have a family history of juvenile polyposis, and the familial cases are associated with germline mutations in *SMAD4* in 15% or *BMPRIA* in 25%.[35,36] These two genes are involved in the TGFß signal transduction pathway. The multiple polyps usually cause severe symptoms of diarrhea, rectal bleeding, and sometimes hypoproteinemia and electrolyte disturbances. Severely affected patients need colectomy or proctocolectomy.[37] In aggressive cases the juvenile polyps persist and multiply in the rectum, or occur in a pelvic or Kock pouch. Topical Sulindac treatment has been effective in controlling juvenile pouch polyps. Regular EGD and capsule endoscopy can be used to assess the severity of upper gastrointestinal involvement.

Other Juvenile Polyposis Syndromes

The other juvenile polyposis syndromes feature a variety of colorectal polyps including juvenile polyps, ganglioneuromas, lipomas, neurofibromas, and the occasional adenoma. The risk of colorectal cancer is not significantly above average, and extra-colonic features of the diseases predominate. Cowden's Syndrome is due to dominant inheritance of germline mutations in a tumor suppressor gene, *PTEN*.[38] A germline mutation in *PTEN* can be found in 80% of patients whose clinical features fir the criteria listed by the International Cowden Consortium.[39] In addition to macrocephaly and other benign features there is an increased risk of thyroid (follicular), breast, uterus and skin cancers.

Bannayan-Ruvalcaba-Riley syndrome is a variant of Cowden's syndrome with which it shares some features (macrocephaly, lipomas). There are also hemangiomas, and a pigmented (speckled) penis.[40] Bannayan-Ruvalcaba-Riley syndrome is also due to mutations in *PTEN*.[41] Gorlin's syndrome has other distinctive extracolonic features including multiple nevoid basal cell cancers, skeletal abnormalities, and cranio-facial abnormalities, and the lowest incidence of gastrointestinal involvement of the hamartomatous polyposes. It is due to a germline mutation in *PTCH*.[42]

Hyperplastic Polyposis

The genotype of hyperplastic polyposis is unknown, but there is increasing evidence of a high cancer risk associated with multiple colonic hyperplastic polyps.[43,44] These polyps are usually large and right sided. The occurrence of similar hyperplastic polyps in some patients and families with HNPCC, and the suggestion of a novel genetic pathway to colorectal cancer involving hyperplastic polyps and serrated adenomas make this a confusing but fascinating area.[45] There is no doubt, however, that several series describe patients where hyperplastic polyposis is strongly associated with colorectal cancer. The role of prophylactic colectomy in this syndrome has not been defined.

Mixed Polyposis Syndrome

The mixed adenoma/hamartoma syndrome has been described in only a few families, with a link to chromosome 15. *CRAC1* is a candidate gene for this syndrome.[46] The families feature a high incidence of colorectal cancer, in a dominant pattern of inheritance. The choice of treatment lies between colectomy and endoscopy.

Surveillance

Patients with FAP need yearly

colonoscopy from diagnosis until surgery, then yearly proctoscopy or pouchoscopy. Regular EGD starts at age 20 years and is then performed every1 to 5 years according to Spigelman Stage. Physical examinations and thyroid exams are performed yearly.[47,48]

Patients with MAP need yearly colonoscopy from diagnosis until surgery, then yearly proctoscopy or pouchoscopy. Regular EGD starts when they are age 20 years and then continues every 1 to 5 years according to Spigelman Stage.

Peutz-Jehger's Syndrome patients begin with colonoscopy , EGD and capsule endoscopy at age 10 years, and then continue with surveillance very 2 years.[49] Breast self exam and mammography begin at age 20 years with BSE continuing every year and mammography every 2 years. Pancreas ultrasound is performed every year from age 30 years and a chest Xray, pelvic exam and ultrasound is done every year from age 20. Finally, a testis exam is performed every year from age 10 years.[31]

Juvenile polyposis patients have colonoscopy starting at age 15 years then yearly until there are no polyps or surgery. Then colonoscopy is done each 2 to 3 years or proctoscopy / pouchoscopy each year. EGD is performed, starting at age 15 years then every 2 to 3 years thereafter.[50]

For patients with Cowden's syndrome, colonoscopy is recommended at age 50 years, and a thyroid ultrasound age 18 years, then yearly. Breast self exam (for both men and women) and mammography is begun at age 25 (bse) and 20 [39](mammography) and continued yearly. Pelvic examination and endometrial biopsies should begin at age 35 years and continue yearly. Finally, physical exam including skin and urinalysis starts at age 18 years and continues yearly.

Patients with hyperplastic polyposis or mixed hereditary polyposis need colonoscopy every 1 to 2 years depending on polyp number and size, from the time of diagnosis until surgery. Then yearly proctoscopy is done.

Role of Registries

The care and coordination of testing and surveillance in families with hereditary colorectal polyposes is complex. Genetic testing involves counseling before and after the test is performed. Surveillance and treatment are performed by multiple specialists. Care of the entire family is best performed in the context of a center, department or registry that has special expertise in the management of these families.[51,52] Such centers of excellence do not assume the day-to-day care of the patient, but rather serve an integrating and facilitating function. In some cases, use is made of the center's particular expertise. In other cases most of the actual clinical care is done by the patient's local physicians. The need for expert counseling, education and advice is always the same however.

Genetic Testing

Testing of DNA for germline mutations is now the preferred way of defining who is affected and who is not, in a family. The genes responsible for many of the polyposis syndromes have been identified and commercial testing is available. Current DNA sequencing technology allows detection of a mutation in at least 90% of FAP patients and a high proportion of patients with MAP, Peutz-Jehger's and Juvenile polyposis. The strategy is to first test an affected relative. Once a mutation is found in someone who is affected, then unaffected at-risk relatives can be tested. If they do not carry the mutation they are excused from further work-up until they turn 50 years old, at which time average population screening for colorectal cancer begins. If they do carry the mutation, then surveillance begins immediately. If a mutation is not found in a clinically affected person, then genetic testing is not useful in that family. Everyone must have colonoscopy.

Genetic testing is best performed in the context of expert genetic counseling, including pretest counseling and post-test counseling.[53] In this way, proper interpretation of the results is ensured and the patient and the family's reaction to the results can be assessed and assisted.

Conclusion

Multiple colorectal polyps are a clue to the possible presence of an inherited syndrome predisposing patients to colorectal cancer. Diagnosis is based on biopsy of a representative

number of polyps, documentation of likely extracolonic manifestations, a careful search of the family, and genetic testing for a germline mutation. Treatment depends on the organs affected, the severity of the polyposis and the nature and severity of symptoms. Lifelong surveillance of all affected family members is recommended.

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