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A RARE CASE OF FAMILIAL ADENOMATOUS POLYPOSIS WITH COLONIC TUMOURS TREATED WITH TOTAL PROCTOCOLECTOMY AND BROOKES END ILEOSTOMY

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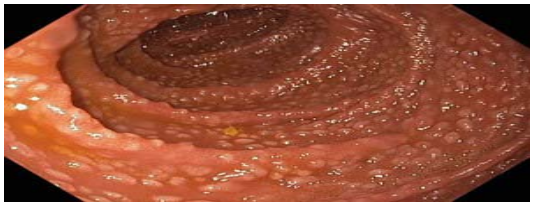
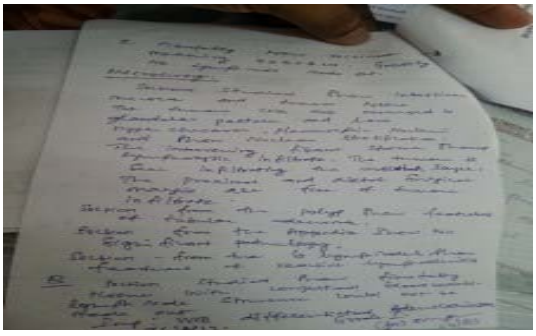
Abstract : Familial Adenomatous Polyposis is a rare disease of the colon, which presents with hundreds of polyps althrough the colon. The disease occurs as a result of various mutations in specific genes and is transmitted in an autosomal dominant fashion in the families. There are many extra intestinal malignancies and manifestations associated with the disease, and many related syndromes which all could predispose to malignancy, not only in the colon but in many other body parts even brain. Screening of the family members, and early colectomy for those who show signs of the disease could prevent early mortality due to the colonic manifestations of the disease. Here we present a case of Familial Adenomatous Polyposis with growths in ascending colon and hepatic flexure which was successfully treated with Total procto colectomy and Brookes end ileostomy.

Keyword : Familial Adenomatous Polyposis, APC gene, colonic polyps, apple core growth, Total Proctocolectomy, Brookes end ileostomy

59 year old male came with complaints of loss of apetite and loose stools since 40 days, abdominal pain and bleeding per rectum since 30 days. He did not give any history of vomiting, fever or melena. He was a hypertensive on treatment since past 3 years. But he did not have any history of tuberculosis, diabetes mellitus, asthma, or any surgery or regular use of other medication in the past. On enquiring about the family, he gave a history that, his own brother had undergone a colostomy and later this brother had died of brain tumour. He had no other siblings and his parents were normal according to the history he provided. On examination, the patient was sick looking, though he was conscious and oriented. He was pale, there was no icterus, cyanosis, clubbing, or pedal edema. There was no generalised palpable lymphadenopathy. His vitals were stable, was afebrile, had a blood pressure of 150/90 mmHg, and pulse was 80/min. Cardio vascular system and respiratory system was normal on examination. He had no focal neurological deficit. On inspecting the abdomen, the shape was scaphoid, all quadrants were moving equally with respiration, umbilicus was normal in position and in shape. There was no visible mass or scar or sinus or dilated vein over the abdominal wall. There was no visible gastric or intestinal peristalsis.



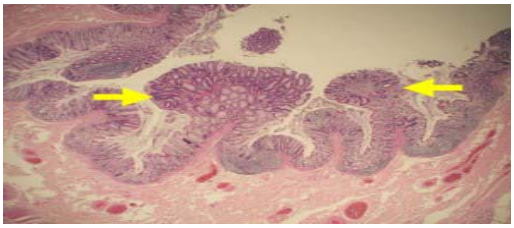
COLONOSCOPIC VIEW OF ADENOMATOUS POLYPS



HISTOLOGY REPORT OF THE BIOPSY

While palpating the abdomen, there was tenderness in right hypochondrium and right lumbar region. There was no guarding, rigidity, organomegaly or palpable mass to be felt. No abnormality was found in percussion, and auscultation revealed normal bowel sounds. External genitalia and testes were found to be normal. Hernial orifices were free. Left supraclavicular fossa was also free. Per rectal examination revealed palpable polyp at 6'o clock position. On proctoscopy, the polyp could be seen at 6'o clock position. Ultrasound abdomen showed, bowel

mass lesion with irregular wall thickening noted in right hypochondrium of size 8.1* 5.2 cm involving ascending colon and hepatic flexure. He also had bilateral medical renal disease and fatty liver. CT scan of the abdomen was done and it showed, Apple Core Growth in distal ascending colon and hepatic flexure measuring 6.78*2.1cm, there was transmural thickening of descending colon and ascending colon with obstruction and proximal dilatation. Multiple colonic polyps in ascending, descending, sigmoid colon, rectum -largest at recto sigmoid junction (0.9*0.6 cm). Also there were paracolic infiltrations with multiple paracolic lymph nodes at ascending colon. Mucosal thickening of pyloric antrum (antral gastritis) with mild adhesions at umbilical region-bowel loops are pasted to anterior abdominal wall. There was no evidence of adrenal/liver secondaries. Both kidneys were slightly shrunken. Thorax had no evidence of lung/mediastinal secondaries.



HISTOLOGY VIEW 1

DISCUSSION

Definition

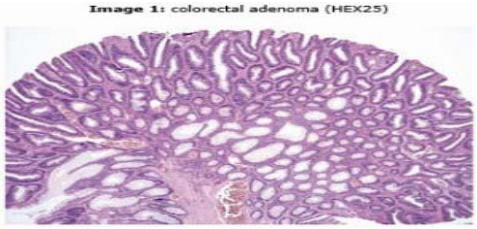
FAP is an autosomal dominant disease that is classically characterized by the development of hundreds to thousands of adenomas in the rectum and colon during the second decade of life. Almost all patients will develop colorectal cancer (CRC) if they are not identified and treated at an early stage. However, today it is unusual for patients to present with CRC as the majority of patients are diagnosed before cancer develops. Attenuated FAP is a milder form that is characterized by fewer adenomas, a later age of adenoma development and cancer diagnosis.

Epidemiology

Worldwide, CRC is a major cause of cancer associated morbidity and mortality. Its incidence varies considerably among different populations with the highest incidence reported from Western and industrialized countries. Worldwide, about 85% of CRCs are considered to be sporadic, while approximately 15% are familial with FAP accounting for less than 1% (Fig. 1). However, FAP is one of the best known and understood genetic diseases. In many countries there are local FAP registries; however it is difficult to obtain accurate nation-wide data. In the UK, Reed and Neel presented a detailed genetic study in 1955 and calculated the incidence of FAP at birth to be 1:8,300 [1]. In 1975, Alm presented an incidence rate of 1:7,645 in Sweden [2]. These estimates were based on clinical criteria before the availability of mutation analysis and recognition of all the clinical variants and differential diagnoses. In 2009, the European Medicines Agency (EMEA) estimated that FAP affected approximately 3-10/100,000 people in the European Union which is equivalent to 11,300 - 37,600 individuals [3]. Clinically, FAP manifests equally in both sexes by the late teens and in the twenties age group.

Clinical description

Symptoms are uncommon in the child and adolescent until the adenomas are large and numerous so as to cause rectal bleeding or even anemia. Other non-specific complaints such as change in bowel habits, constipation, or diarrhea, abdominal pains or palpable abdominal masses or weight loss in young patients can lead to recto-sigmoid examination and identification of polyps suggestive of FAP. FAP can present with extraintestinal manifestations such as osteomas, dental abnormalities (unerupted teeth, congenital absence of one or more teeth, supernumerary teeth, dentigerous cysts, and odontomas), congenital hypertrophy of the retinal pigment epithelium (CHRPE), desmoid tumors, or extracolonic cancers (thyroid, liver, bile ducts, central nervous system), (see below). Some lesions (skull and mandible osteomas, dental abnormalities, fibromas on the scalp, shoulders, arms, and back) are indicative of the Gardner variant of FAP. Today the condition should rarely present as a colonic or even as an extra-colonic malignancy.



HISTOLOGY VIEW 2

Colonic manifestations

Classic FAP is characterized by the presence of hundreds to thousands of colorectal adenomas of different sizes. Today this is rarely seen in countries with well developed public health services. In the majority of patients polyps begin to develop during childhood, mostly in the distal colon (rectosigmoid) as small intramucosal nodules (Fig. 2A). By the time of adolescence, the polyps are usually identified throughout the colon and, thereafter, increase in size and numbers (Fig. 2B). About half of FAP patients develop adenomas by 15 years of age and 95% by age 35 years [4]. Generally, cancers start to develop a decade after the appearance of the polyps. So, if the colon is left intact, the majority of patients with FAP eventually develop CRC by the ages 40-50 years. However, it should be emphasized that, although uncommon, CRC can develop in children or in older adults.

In the stomach, *fundic gland polyps* (FGP) develop in 90% of patients with FAP. They are of special interest since, in contrast to the benign nature of sporadic FGP, 40% of these lesions in individuals with FAP have been shown to have adenomatous features, but rarely do progress to cancer [5]. FGPs in FAP patients are pathogenetically distinct from sporadic FGPs. Somatic, second-hit *APC* gene alterations, which precede morphological dysplasia in many FAP-associated FGPs, indicate that FGPs arising in the setting of FAP are neoplastic lesions [6]. *Adenomatous polyps in the duodenum* (mainly in the 2nd and 3rd parts) and *periampullary region*. In one series they developed in approximately 90% of individuals with FAP, 10-20 years after diagnosis of colorectal polyps [7]. The lifetime risk of duodenal adenomas has been reported to reach 100% [8, 9]. Spigelman's classification of duodenal polyps is a scale, based on polyp number, size, histology, and severity of dysplasia (Table 1). It is estimated that about 5% of duodenal, and specifically periampulary polyps, progress to cancer within 10 years [10]. While rare in the general population, the risk of duodenal or periampullary cancer is increased several hundred fold in FAP patients [7]. Duodenal polyposis usually progresses in an orderly fashion through increasing Spigelman stage [7], but cancer can present in patients under surveillance with lower Spigelman stages being identified in their penultimate examinations [10-12]. Pancreatitis can be the result of ampullary adenoma or as a presentation of malignancy. *Small bowel adenomas*. It is well known that

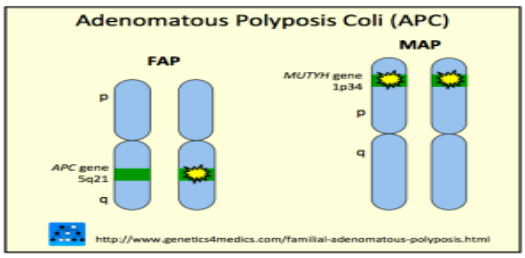
individuals with FAP carry a risk of small bowel polyps and even cancer although at a much lower rate than duodenal and ampulary neoplasms. The exact incidence of small bowel polyps is unknown and is generally dependent on the examining methodology used for evaluation. Bertoni G *et al.*, in 1993, studied 16 patients with FAP by push enteroscopy and detected jejunal polyps in 50% of subjects [13]. Later, with the use of double balloon enteroscopy or capsule endoscopy, the rate of jejunal and ileal polyps was estimated to be between 30-75% [14-16]. The rate of small bowel malignancy is much lower than ampullary or duodenal cancer. However, the treating physician should be aware of this possibility and be ready to implement surveillance, which will be discussed.

Etiopathogenesis

FAP is a genetic disorder resulting from a mutation in the adenomatous polyposis gene (*APC*) gene. Most FAP patients have a family history of colorectal polyps and cancer, however, 25-30% of them are "*de novo*", without clinical or genetic evidence of FAP in family members [26,27]. It is now recognized that this can be partially explained by being the result of germline mosaicism [28]. Classic FAP is inherited as an autosomal dominant trait and results from a germline *APC* mutation; AFAP is mostly caused by specific *APC* mutations. A subset of individuals with clinical features of FAP will instead carry a mutation in the *MUTYH* gene (to be discussed later).

The APC gene in brief

APC is a tumor suppressor gene located on the long arm of chromosome 5 in band q21 (5q21). The coding region is divided into 15 exons and encodes a large protein (309 kilo-Daltons) [29]. The *APC* protein has multiple domains that mediate oligomerization as well as binding to a variety of intracellular proteins, which have an important role in cell adhesion, signal transduction and transcriptional activation.



Normal APC structure and functions

The *APC* gene spans a region of 108,353bp (NC_000005). The mRNA is 10,719 bp long (NCBI# MN_000038) and has 16 exons. The mRNA codes for a protein of 2,843 amino acids long with a molecular weight of 310 kDa (NCBI# NP_000029). Most of the amino acids are in the last exon (exon-16 that is 8,689 bp long with 6,574 bp coding sequences). Only exons 2-15 are coding exons and have 653 amino acids and exon 16 has 2,190. *APC* is a classical tumor suppressor protein that plays a central role in Wnt signaling, in part by regulating the degradation of -catenin. Wnt signals influence the stability of a protein complex containing -catenin, conductin and GSK3 (glycogen synthase kinase 3). In the absence of Wnt or the presence of wild-type *APC* protein, -catenin is degraded. In the presence of Wnt, or the absence of *APC* (as occurs in many colon cancers), -catenin target genes including c-*myc* are expressed. *Myc* expression, in turn, leads to the expression of the polyamine ornithine decarboxylase (ODC) which is a proto-oncogene (Fig. 6). The *APC* gene product indirectly regulates transcription of a number of critical cell-proliferation genes, through its interaction with the transcription factor -catenin. *APC* binding to -catenin leads to ubiquitin-mediated -catenin destruction; loss of *APC* function increases transcription of -catenin targets. Homozygous *APC*truncation has been shown to affect chromosome attachment in cultured cells. Roles for *APC* in cell migration have been demonstrated *in-vitro* and in mouse models.

Disturbed APC structure and functions in brief

More than 300 different types of mutations are recognized today as the cause of FAP. Most of these mutations (insertions, deletions, nonsense mutations, *etc.*), result in a truncated protein. The most common mutation, occurring in about 10% of FAP patients, is a deletion mutation in codon 1309, the next most common, occurring in 5% of the patients, is a deletion at codon 1061.

Genotype-phenotype correlations in brief

Some correlation does exist between the sites of specific genetic mutations and the clinical manifestations of the disease, however, this correlation is not exact and differences do occur (to be discussed later) [35,36] (Fig. 7). Mutations contributing to classical FAP occur between exon 5 and the 5' portion of exon 15, whereas those associated with AFAP tend to cluster in the extreme 5' portion of the gene and the 3' portion of exon 15 proximal to codon 1517 or distal to codon 1900 [35, 36]. Mutations between codons 1250 - 1464 are associated with profuse polyposis. Mutations at specific positions can cause CHRPE [37]; it is almost always absent if the protein-truncating mutation in the *APC* gene occurs before exon 9, but is consistently present if it occurs after this exon. Patients with a mutation between codons 1445 - 1578 do not express CHRPE, but can develop severe desmoid tumors [38].

Diagnosis

The diagnosis of classic FAP is based on a suggestive family history and clinical findings. Whenever possible, the clinical diagnosis should be confirmed by genetic testing.

Clinical diagnosis

The clinical diagnosis is dependent on the physician's suspicion and awareness. The patient may be completely asymptomatic and obtaining a detailed **family cancer history** is essential for a correct diagnosis, since in most cases some grandpa rents, parents and siblings will be affected. Asking simple questions like "has anyone in your family had cancer? Which cancer? And at what age?" is important information. Alternatively, rectal bleeding or abdominal complaints may develop depending on the stage of disease *i.e.*, polyp burden or stage of cancer. For the astute physician, identification of extra-colonic manifestations can lead to performing endoscopic examination of the large bowel. For example, identifying a desmoid or a mandibular osteoma in an individual should lead to a work-up for ruling-out FAP. This should initially be done by taking a detailed extended family history and performing a sigmoidoscopy or a full colonoscopy depending on the age of the patient or whether we suspect FAP or AFAP. During childhood, only diminutive adenomas may be found, limited mainly to the rectosigmoid area of the colon, by a *flexible sigmoidoscopy* (Random biopsies can visualize intra-mucosal adenomas As age progresses, hundreds of colorectal adenomas and, in some patients, adenomas in extracolonic locations may be found (as described previously) (The diagnosis of AFAP is more complex than that of classic FAP because of the wide phenotypic variation of disease. Total colonoscopy, rather than sigmoidoscopy, has been advocated for screening individuals at risk as the polyps tend to have a right-sided distribution [25]. Chromoendoscopy (is recommended to highlight the polyp burden. As in FAP, the diagnosis of AFAP is based on the combination of clinical findings and genetic tests. Genetic testing is mainly used for screening and the presymptomatic early diagnosis of at-risk family members. In addition, confirmation of the diagnosis in

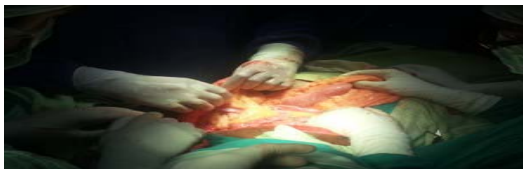
patients with obscure clinical findings is essential. At first, only the index case should be tested and because of the long time it can sometime take to receive the answer to the initial mutation analysis, and even if no mutation is identified, firstdegree relatives should be managed clinically until results are obtained. If the mutation has been identified, it can be quickly and cheaply performed to screen at -risk relatives.

Differential diagnosis of FAP

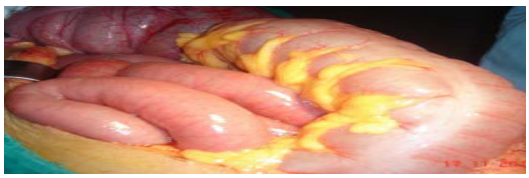
There are other disorders causing multiple polyps. These include hamartomatous polyps such as those in Peutz-Jeghers syndrome (mainly in the small bowel but may occur anywhere along the gastrointestinal tract), familial juvenile polyps or hyperplastic polyposis and hereditary mixed polyposis syndromes. Multiple lymphoid aggregates can masquerade as early FAP, especially in children and young adults. The diagnosis depends on the correct histological classification of the polyps. Dysplastic changes occurring in a non-adenomatous polyp can be mistakenly identified as a multiple adenoma syndrome compatible with FAP. The combination of adenomatous polyps and an autosomal dominant pattern of inheritance is classic for FAP and rules out most of the alternative possibilities. At times it is difficult to differentiate between AFAP and Lynch syndrome (hereditary non polyposis colorectal cancer as both may have a low polyp burden, occurring mainly in the right colon. The differentiation from MAP is discussed above.

Management of the FAP patient

Cancer prevention and maintaining good quality of life are the main goals in management of patients with clinical or genetic evidence of FAP. Large bowel endoscopy is the most important clinical examination since there is almost a 100% chance of CRC. However, as discussed previously, the disease is systemic with extracolonic manifestations and should be looked for by systematic reexaminations. CRC is rare in the asymptomatic youth, so after their genetic diagnosis and baseline sigmoidoscopy, they are systematically followed clinically until completing schooling and growth and maturing. Around ages 16-18 y patients with FAP should be followed by annual or less frequent colonoscopic examinations (depending on the polyp burden at last colonoscopy) and all significant sized adenomas should be removed if surgery is not contemplated at that time. In addition, both forward-viewing and side-viewing upper tract endoscopies should be performed prior to surgery or every 1 to 5 years depending on the polyp burden and Spigelman stage (Tables 1 and 2) [] to detect gastric but mainly duodenal and periampullary adenomas, respectively. Usually, by the late teens or early twenties, due to the increasing number of adenomas, *prophylactic cancer-preventive colorectal surgery* is advocated []. Since this is an elective procedure the timing can be arranged to be the least inconvenient for the patient and family. Elective surgery, can at times, be delayed if the patient is compliant and polyps are sparse and not large. Surgical options include subtotal colectomy with *ileorectal anastomosis* (IRA), total proctocolectomy with *ileostomy*, and proctocolectomy with or without mucosectomy and *ileal pouch anal anastomosis* (IPAA)

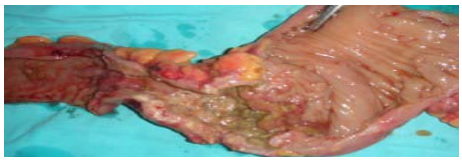


DILATED BOWEL LOOPS-INTRA OP



Since restorative proctocolectomy (RPC) with ileal-pouch anal anastomosis (IPAA) removes the entire diseased mucosa, it has become firmly established as the standard operative procedure of choice for familial adenomatous polyposis (FAP). Many technical controversies still persist, such as mesenteric lengthening techniques, close rectal wall proctectomy, endoanal mucosectomy vs. double stapled anastomosis, loop ileostomy omission and a laparoscopic approach. Despite the complexity of the operation, IPAA is safe (mortality: 0.5-1%), it carries an acceptable risk of non-life-threatening complications (10-25%), and it achieves good long-term functional outcome with excellent patient satisfaction (over 95%). In contrast to the high incidence in patients operated for ulcerative colitis (UC) (15-20%), the occurrence of pouchitis after IPAA seems to be rare in FAP patients (0-11%). Even after IPAA, FAP patients are still at risk of developing adenomas (and occasional adenocarcinomas), either in the anal canal (10-31%) or in the ileal pouch itself (8-62%), thus requiring lifelong endoscopic monitoring. IPAA operation does not jeopardise pregnancy and childbirth, but it does impair female fecundity and has a low risk of impairment of erection and ejaculation in young males. The latter can almost completely be avoided by a careful "close rectal wall" proctectomy technique. Some argue that low risk patients (e.g. <5 rectal polyps) can be identified where ileorectal anastomosis (IRA) might be reasonable. We feel that the risk of rectal cancer after IRA means that IPAA should be recommended for the vast majority of FAP patients. We accept that in some very selected cases, based on clinical and genetics data (and perhaps influenced by patient choice regarding female fecundity), a stepwise surgical strategy with a primary IPA followed at a later age by a secondary proctectomy with IPAA could be proposed.

POST OP SPECIMEN



Post-colectomy surveillance

It is important to emphasize that follow-up is vital after surgical procedures are completed. Initially, it should be at short intervals to asses the psychological and physical adaptation to surgery and identify desmoid tumor formation in its earliest stage. The initial follow-up should include a thorough physical examination, baseline abdominal ultrasound (US) or computed tomography or magnetic resonance imaging (CT or MRI) to aid in detecting existing or future changes suspicious of a desmoid tumor. Patients after stapled and hand sewn IRA are at risk for rectal adenomas and carcinomas. Therefore, the physician needs to stress the importance of endoscopic annual surveillance of the pouch. Many studies have shown that adenomas and occasionally even adenocarcinomas have been found in the ileo-anal pouch

after restorative proctocolectomy (Therefore, surveillance of the pouch [and transitional anal zone is essential.

Quality of life after surgery

Since surgery is an elective procedure in FAP, the treating specialist has the opportunity to educate the patient regarding the specific procedure and quality of life that should be expected post-surgery so as to minimize fear and reduce expectations. This can be facilitated by meeting patients of the same sex and similar age group who have had a similar procedure performed, and occasionally a sympathetic psychologist can be helpful in overcoming fear [There are many reports showing that most patients are satisfied following an IPAA procedure [However, patients should be advised that although fecal elimination via the anus will be preserved, functional outcome may vary and is not comparable with bowel elimination prior to surgery. Pouchitis is a major cause of morbidity and discomfort in patients undergoing IPAA for ulcerative colitis (15-20%), however, this is rare in FAP patients (0-10%). The majority of patients with FAP develops adenomatous polyps and requires preventive surgery during their late teens or early twenties. These years are the main reproductive years and maintaining sexual function is of major concern. Sexual impairment following proctectomy is largely techniquedependent and this should be discussed with the surgeon performing the procedure . For men, denervation of the pelvic plexus is the major cause of erectile and ejaculation dysfunction. Following an IPAA, erectile dysfunction is reported to occur in 0-1.5% of patients, while ejaculation dysfunction occurs in 3-4% of these individuals In woman, sexual dysfunction is less obviously disturbed, mostly due to the fact that it is more difficult to measure.

In addition, there is a lack of reporting of discomfort as well as dysfunction. Dyspareunia is a major concern and in different reports affects between 3-22% of the patients [This may be due to anatomical changes within the pelvis following proctectomy. Approximately 3% of woman report avoidance of sexual contact due to fear of fecal leakage. For these reasons surgical experience with the IPAA procedure is of great importance and patients with FAP are advised to have the procedure performed in medical centers that are familiar with FAP and by surgeons experienced with this procedure. Knowledge about fertility of women suffering from FAP is scarce and inconclusive. The IPAA procedure does not risk pregnancy but may reduce fertility. Olsen in 2003 [reported that fecundity dropped to 54% following proctocolectomy with IPAA, a rate similar to that in patients undergoing IPAA for other indications although it was greater than the postoperative fecundity of women with ulcerative colitis. It is thought that pelvic adhesions after surgery may be responsible for infertility in FAP woman post IPAA. The significant reduction in female fecundity after IPAA should be discussed with women with FAP before it is decided which surgical option to choose and timing of the operation. If the mild manifestation of FAP make it possible, and the patient is compliant for frequent follow-up, then elective surgery should be delayed until completing the planned family.

Effectiveness of screening

The usefulness of screening asymptomatic FAP patients for all of its possible manifestations is unproven. For children, to identify hepatoblastoma, some recommend annual alpha-fetoprotein and abdominal ultrasound from birth until the age of 10 years. For all FAP patients, an annual physical examination should include an evaluation for soft tissue or bone lesions, and a thorough thyroid examination with a low threshold for performing an ultrasound of any suspicious lesion. Symptomatic patients (abdominal pain, new onset diabetes mellitus or acute pancreatitis) require evaluation which could include computed tomography of the abdomen to rule out desmoid tumors of the mesentery or pancreatic adenocarcinomas (or intraductal papillary and mucinous tumors (IPMT) of the pancreas [If the CT is not diagnostic, then magnetic resonance imaging is indicated, it can outline vascular involvement of a desmoid tumor and may predict its growth[CT of the brain can also be used in symptomatic patients to search for a medulloblastoma. Individuals with a *family history* of FAP should be screened. When a specific *APC* mutation has been identified in an index patient all 1st degree relatives carry a 50% risk of FAP and should be referred for genetic counseling and offered *APC* mutation testing. A family member who is found to carry the mutation has 100% chance of developing FAP and its complications. It is recommended that these individuals have a colonoscopy and follow specific surveillance recommendation that have been outlined for FAP patients. Children that have been identified as carrying an *APC* mutation should have a flexible sigmoidoscopy performed by the age of early adolescence unless symptoms develop at an earlier stage. When polyps are detected, discussion with the patient and parents should take place regarding further surveillance and timing of surgery as described above. If genetic testing cannot be performed in a 1st degree relative of a known mutation carrier, then the asymptomatic 1st degree family member has a 50% chance of harboring the mutation and should be screened as if they have the *APC* mutation. All adults should have colonoscopies performed and all children should undergo a flexible sigmoidoscopy around the age of 10-12 years [Adenomas develop with the child's growth, and therefore are easier to identify at adolescence. If polyps are not found, then there should be annual clinical visits for physical or ophthalmic evidence of FAP and to assess suspicious symptoms.

Sigmoidoscopy should be repeated at suitable intervals, minimizing its psychological trauma and maximizing cooperation of the growing child, until polyps emerge. If by the age of 25 years polyps are not detected, then biennial sigmoidoscopy or, preferably colonoscopy, can be done since the likelihood of developing adenomas decreases as the patient's age increases. From the age of 35 years, an examination every third year is recommended until the individual is 50 years old. If polyps have not been detected by then, the individual most likely, but not absolutely, doesn't have FAP, and screening is recommended according to guidelines for the general population. When an individual in a family with a known mutation tests negative, then routine colorectal screening is recommended, as for the general population, beginning at age 50 years. In approximately 25-30% of patients with clinically evident FAP a mutation cannot be identified. If available, *MUTYH* testing and more complete DNA analyses are performed in specialized laboratories. If these are also negative, then such individuals are considered to have FAP and should be treated as such. Gene testing can exclude FAP only if a mutation is identified in a family member and this mutation does not exist in a given individual.

Prevention

Diet and lifestyle

The evidence for being able to modulate the clinical manifestations of a dominant genetic disease is indirect and based on observations in animal models and humans. Caloric restriction or diet with olive oil, fruits and vegetables significantly reduced the number of polyps in the genetically manipulated *APC* Min mice model [In the same model, low dosage ursodiol together with sulindac prevented adenomas with less toxicity than if each had been given alone in full dosage]. Clinical observation of FAP families showed that the severity of disease varied between affected family members or between families carrying the same mutation [This would suggest that not only are there genetic-genetic/endogenous modulating factors, but there could be genetic-exogenous modulating

factors at play. Adenoma expression and growth occurs with aging, effect of growth factors, hormones, weight gain, diet, tobacco use. As an example, in two twin boys with FAP there was a clear correlation between obesity in one twin and adenoma expression as compared to the other twin (Rozen, personnel communication). So, it would be wise to recommend a "balanced" CRC-preventive lifestyle and diet from childhood in anticipation of modulating the clinical expression of FAP.

Chemoprevention

Randomized trials have shown that both sulindac [and celecoxib cause regression of established adenomatous polyps in individuals with FAP. Specific cycloxygenase-2 (COX-2) inhibitors, celecoxib and rofecoxib [], among others, were developed to overcome the risk of gastrointestinal damage due to inhibiting the cytoprotective COX-1. In patients with FAP, treatment with 400 mg of celecoxib twice daily for 6 mo had been shown to reduce the tumor burden by 28% as compared to a reduction of 4.5% in the placebo group ($p = 0.003$) [In 2001, the US Food and Drug Administration approved the use of celecoxib (as an adjunct to endoscopic surveillance, and surgical management) in patients with FAP and having polyps; while the European Medicines Agency approved an orphan designation for celecoxib [3]. This agency has also designated eflornithine hydrochloride, an irreversible inhibitor of ornithine decarboxilase (ODC), the first and rate-limiting enzyme in the polyamine synthesis, as an orphan medical product to be investigated for use in individuals with FAP

Prognosis

The goal is pre-symptomatic genetic diagnosis of *APC* mutation-carriers that can lead to improved clinical care and prevent premature mortality from cancer or other FAP complications. Most patients with clinical FAP can be identified and have their diagnosis confirmed by genetic testing. Individuals with FAP carry a 100% risk of colorectal cancer that is reduced almost absolutely when patients enter a screening-treatment program as outlined earlier. Once proctocolectomy has been performed, the risk of ampullary and duodenal cancer is significant and requires lifelong upper gastrointestinal surveillance that has been shown to save lives of FAP patients. Desmoids need to be identified early while small and not causing local perturbations. They should be managed as described above. Duodenal cancer and desmoids are the two main causes of mortality after total colectomy has removed the risk for CRC. The sociological, psychological and physiological issues related to the diagnosis and treatment of FAP need to be addressed. The colectomy and ensuing change in bowel habits, frequently lead to dietary changes that can be unbalanced and lead to vitamin-mineral deficiencies. Notable is the possibility of vitamin B12 deficiency due to rapid intestinal transit, ileal resection and ascending bacterial overgrowth. All these problems require systematic follow-up and supportive care.

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