Familial adenomatous polyposis : clinical presentation, detection and surveillance

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Abstract

Colorectal cancer (CRC) is a leading cause of cancer related death in the western countries. It remains an important health problem, often under-diagnosed. The symptoms can appear very late and about 25% of the patients are diagnosed at metastatic stage. Familial adenomatous polyposis (FAP) is an inherited colorectal cancer syndrome, characterized by the early onset of hundred to thousands of adenomatous polyps in the colon and rectum. Left untreated, there is a nearly 100% cumulative risk of progression to CRC by the age of 35-40 years (1,2), as well as an increased risk of various other malignancies. CRC can be prevented by the identification of the high risk population and by the timely implementation of rigid screening programs which will lead to special medico-surgical interventions. (Acta gastroenterol. belg., **2011**, 74, **415-420**).

Epidemiology

Familial adenomatous polyposis (FAP) is an autosomal dominant family cancer syndrome, caused by germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21 (3). It is responsible for less than 1% of all CRC cases (4). Twenty to fifty percent of FAP patients worldwide were reported to have non-detectable *APC* mutations (5-7). Several polyposis registries such as the Swedish and the Japanese showed that the mean age of subjects with CRC at diagnosis was approximately 40 years (8,9). For asymptomatic relatives, the mean age of FAP diagnosis was respectively 22 and 28 years.

Clinical presentation and associated malignancies

Lower GI tract polyps and cancers

The most frequent feature of FAP is the development of hundreds of adenomatous polyps in the colon and rectum usually in adolescence with an almost inevitable progression to CRC by the age of 35-40 years, significantly younger than sporadic cancers. The preferred localization of tumours is the left side of the colon where 70-80% of the tumours occur (8).

Upper GI tract polyps and cancer

Upper GI polyps (gastric and duodenal adenomas) are present in nearly 90% of FAP patients by the age of 70 years (10). Two-thirds of duodenal adenomas occur in the papilla or periampullary region (11). Advanced duodenal adenomas confer an increased risk of small bowel cancer, which is the third leading cause of death in FAP patients (8.2%), in addition to CRC (58.2%) and desmoid tumours (10.2%) (12). Although still relatively rare, the risk of periampullary or duodenal cancer in FAP patients is several hundred-fold greater that in the general population. The lifetime risk of upper GI cancer is estimated at approximately 5% (13). The cumulative risk increases with age, therefore, it remains important to perform routine upper endoscopic surveillance with random biopsies even in the absence of visible lesions since the incidence of microadenomas is high (14).

FAP patients are also at increased risk for fundic gland polyps in the stomach, with an estimated incidence of 26-61% (15-18), compared with 0.8-1.9% incidence in the general population (19,20). Although these polyps are typically benign lesions in the general population, up to 25% of those in FAP patients show foveolar dysplasia (21), and cases of gastric carcinoma, which is uncommon in whites, associated with diffuse fundic gland polyps have also been reported (22-25).

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Congenital hypertrophy of the retinal pigment epithelium

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) refers to the presence of characteristic pigmented fundus lesions that are thought to occur in 70-80% of patients with FAP (26-28). The presence of multiple bilateral lesions appears to be a highly specific marker for FAP (95-100% specificity) (29). This makes ophtalmological examination an attractive non invasive and early diagnostic test for at-risk family members, beside genetic analysis. CHRPE lesions can also help in predicting the mutation site, since they are restricted to a specific mutation subgroup along the *APC* gene (30).

Desmoid tumours

Desmoids are rare, histologically benign but locally invasive tumours. These tumours are a major cause of morbidity, and the second leading cause of death in FAP patients (12). The overall prevalence of desmoid disease in FAP varies between 12 and 17% (31,32). They tend to be located intra-abdominally (up to 80%), usually involving the small bowel mesentery, or in the abdominal wall and occur after prior abdominal surgery (31, 33,34). Patients with *APC* mutations located between codons 1310 and 2011 appear to be at increased risk of desmoid tumours (35). Most tumours are solitary and can cause abdominal pain, bowel obstruction or perforation, ureteric obstruction, intestinal hemorrhage or even enterocutaneous fistula formation (32). Even today, treatment remains a challenge. Surgical excision carries the risks of bleeding and short bowel syndrome with a recurrence rate as high as 45% (36). Nonsteroidal anti-inflammatory drugs (NSAIDs such as sulindac) and antiestrogens have been used, but less than a third of the tumours stabilize or regress (34,36). Tamoxifen or other antiestrogens may be considered when tumours are slow growing or mildly symptomatic (37). Treatment by chemotherapy or radiotherapy has also been disappointing. Because of the rarity and highly variable natural history of desmoids, efforts to establish uniformity in staging of the disease will be essential for developing definitive trials and effective therapies (38).

Imatinib mesylate (Glivec®) might have activity against desmoid tumours, most likely because of PDGFRB tyrosine kinase activity inhibition, and warrants further study (39,40).

Thyroid cancer

The estimated incidence of thyroid cancer associated with FAP is 1-2% (41,42). The average age at diagnosis is between 23 and 35 years, with a majority of females (17:1) (41,43). These tumours, which are mostly of the papillary type, tend to be well circumscribed, non aggressive, with a low metastatic potential and low 10-year mortality (43). Aside from recommended regular physical examinations of the thyroid gland, there is ongoing debate about the need for additional radiological screening, because of the rarity and excellent long-term prognosis of these tumours.

Hepatoblastomas

The incidence of hepatoblastoma among children of FAP patients is 1 in 235, compared to 1 in 100.000 in the general population (44). As with sporadic hepatoblastomas, boys within FAP kindred are particularly at risk (45).

Other extracolonic malignancies

Other extraintestinal cancers associated with FAP include adrenal, pancreatic, and biliary tract malignancies (46).

Specific Variants of FAP

Gardner syndrome

Gardner's syndrome is a variant of FAP, also resulting from *APC* mutations, in which affected patients present with osteomas and epidermoid cysts in addition to colorectal polyps (47).

Turcot syndrome

Turcot syndrome is characterized by the presence, beside the colorectal polyps, of central nervous system neoplasms, typically meduloblastomas (48).

Multiple colorectal adenoma syndromes

Attenuated FAP

Attenuated FAP (AFAP) is a less severe form of FAP, in which patients manifest with less than 100 polyps, a more proximal colonic location of adenomas, and delayed age of CRC onset (the age of diagnosis is approximately 15 years later than patients with classic FAP). Some attenuated FAP patients have been found to have germline mutations in extreme 5' and 3' ends of the *APC* (49,50). The cumulative risk of CRC by the age of 80 years is estimated to be 69% (51). Patients often have no family history of polyps or CRC, and lack extracolonic features, apart from fundic gland polyps which are quite common and duodenal adenomas (52).

MUTYH associated polyposis

In recent years, biallellic mutations in the base excision repair gene, *MUTYH*, have been detected in a small proportion of attenuated FAP patients with no detectable *APC* mutations (53). *MUTYH* mutations have not been reported in FAP patients with clear autosomal dominant inheritance and classical polyposis. *MUTYH*-associated polyposis shows an autosomal recessive pattern of inheritance, and often presents as attenuated polyposis (54). The life-time risk of CRC is probably less than 50%.

Table 1. – **Surveillance and Follow-up of FAP patients**

Tumour	Procedure	Beginning	Interval
	Clinical evaluation		Yearly
Colon	Sigmoïdo- of coloscopy	10-12 years	Every two years
Upper GI	Gastroscopy	20-25 years	6 months to 4 years
Thyroïd	Clinical evaluation +/- echographic evaluation	10-12 years	Yearly
Hepatoblastoma	Liver palpation, alpha-foetoprotein, echography	Birth	Yearly, until 7 years

Screening and surveillance

Screening of patients and family members, with timely treatment of affected individuals, has led to a significant reduction in the occurrence of CRC at diagnosis of FAP, and an improvement in cumulative survival for all FAP patients (55). It is important to mention that about 30% of the polyposis cases originate from *de novo* mutations in the *APC* gene. These patients are the first individuals in the family to be affected and therefore have a negative family history for polyposis. As a consequence, in sporadic cases displaying a typical polyposis phenotype genetic testing is warranted (56). The recommendations are summarized in table 1.

The current recommendations of the American Gastroenterological Association comprise performing an annual sigmoïdoscopy, beginning at the age of 10-12 years for patients with a genetic diagnosis of FAP and at-risk family members, both individuals that have inherited the *APC* gene mutation as well as relatives who decline molecular genetic analysis (57). More recent guidelines underlined the fact that an interval of 2 years between normal sigmoidoscopies is appropriate. If adenomas are detected, colonoscopic investigations should be performed annually until colectomy is planned (58). Conversely, family members that have not inherited the *APC* mutation display the general population risk for CRC and can be reassured. They are encouraged to participate in population based cancer surveillance programs. At-risk individuals belonging to families with an AFAP phenotype should undergo colonoscopic screening due to the proclivity of colonic adenomas to be located proximally in this variant (59). Periodic examination is recommended starting from age 18-20 (58). Patients who are established carriers of the *APC* gene mutation or in which adenomatous polyposis was diagnosed on sigmoïdoscopy should undergo full colonoscopy to establish the severity of polyposis (60).

After colectomy, endoscopic surveillance in the rectal segment at 6-month to 1-year intervals is recommended (61). With increasing numbers of adenomas, frequency of surveillance should be increased and polyps larger than 5 mm should be removed with a snare. The development of severe dysplasia or villous adenoma not manageable by endoscopic removal is an indication for proctectomy (60).

Management of the upper GI cancer risk is one of the greatest challenges that face clinicians involved in the care of polyposis families, and with improved survival following prophylactic colectomy, the burden of foregut disease will increase. The efficacy of screening is yet to be fully demonstrated. Most authors recommend viewing endoscopies of the stomach, duodenum and periampullary region, beginning at 25-30 years, every 6 month to 4 years depending on the polyp burden (14,62). The purpose is to monitor for the development of high-grade dysplasia, rather than the removal of all visible polyps. The adenomas showing high-grade dysplasia, villous changes, ulceration or a size larger than 1 cm should be removed. The systematic use of coloration with indigo carmine dye and routine biopsies of the duodenal papilla was also advocated by some authors (62). This practice has not yet been largely developed but new strategies and treatment algorithms for duodenal adenomatosis in FAP are expected to become available (13). Endoscopic ablation is a reasonable initial approach for most patients without invasive cancer or as definitive therapy for patients unfit for duodenal resection. For patients with persistent or recurrent high-grade dysplasia in papillary or duodenal adenomas, and for patients with Spigelman stage IV disease (see Table 2, 63), pancreas-preserving duodenectomy or pancreaticoduodenectomy is recommended (64).

Concerning thyroid cancer, a single thyroid palpation in the routine physical examination seems to be sufficient to detect abnormalities (41).

There are no standard guidelines for the detection of hepatoblastomas in children of FAP parents because genetic counselling begins at the age of 10-12 years and mutations are not detected before having a clinical impact on the management of the FAP. Others propose to follow the children for hepatoblastoma from birth until 7 years (61). This attitude supposes a molecular investigation from childhood.

Chemoprevention

A number of NSAIDs, including sulindac, celecoxib, rofecoxib and the sulindac metabolite, exisulind, can reduce polyp number and size in patients with FAP (65-67). However, the long-term use of chemoprophylaxis as primary treatment of FAP is not recommended. These

Table 2. – **The Spigelman Classification for Staging Duodenal Polyposis (adapted from Guillem *et al.* (62))**

Characteristic	1	2	3
No. of polyps	1-4	5-20	> 20
Polyp size, mm	1-4	5-10	> 10
Histologic type	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0, 0 points, Stage I : 1-4 points, Stage II : 5-6 points, Stage III : 7-8 points, Stage IV : 9-12 points.

medications require continued compliance and are not without adverse event (68). Currently, none of the chemoprevention strategies should replace screening, and is an adjunct to endoscopic surveillance, to reduce the rectal polyp burden (58). Moreover, chemoprevention has not been proven effective in the management of duodenal adenomas.

Summary and conclusions

FAP is associated with multiple colonic adenomas which occur at an early age, and proliferate throughout the colon, with malignant degeneration in most patients by the age of 40 to 50 years. Almost all patients affected by FAP will develop foregut as well as hindgut polyps, and duodenal cancer constitutes one of the leading causes of death in screened populations. Without prophylactic colectomy, FAP patients predictably develop colorectal cancer, but the lifetime risk of upper gastrointestinal cancer is lower, estimated at approximately 5%. Management of the upper gastrointestinal cancer risk is one of the greatest challenges that face clinicians involved in the care of polyposis families, and with improved survival following prophylactic colectomy, the burden of foregut disease (particularly duodenal adenomatosis) will increase. The screening and the surveillance of those patients is very important and should be adapted, depending of the genetic feature of each family. Identification of the genes that cause these colon cancer syndromes, coupled with additional insights into their clinical course, has led to the development of specific management guidelines and genetic tests that can diagnose these familial disorders. These guidelines can be life-saving, not only for the affected patient, but also for their family members.

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