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Extra-Intestinal Manifestations of Familial Adenomatous Polyposis

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Familial adenomatous polyposis (FAP) is an autosomal dominantly inherited disorder, which results from a germ line mutation in the APC (adenomatous polyposis coli) gene. FAP is characterized by the formation of hundreds to thousands of colorectal adenomatous polyps. Although the development of colorectal cancer stands out as the most prevalent complication, FAP is a multisystem disorder of growth. This means, it is comparable to other diseases such as the MEN syndromes, Von Hippel-Lindau disease and neurofibromatosis. However, the incidence of many of its clinical features is much lower. Therefore, a specialized multidisciplinary approach to optimize health care—common for other disorders—is not usually taken for FAP patients. Thus, clinicians that care for and counsel members of high-risk families should have familiarity with all the extra-intestinal manifestations of this syndrome. FAP-related complications, for which medical attention is essential, are not rare and their estimated lifetime risk presumably exceeds 30%. Affected individuals can develop thyroid and pancreatic cancer, hepatoblastomas, CNS tumors (especially medulloblastomas), and various benign tumors such as adrenal adenomas, osteomas, desmoid tumors and dental abnormalities. Due to improved longevity, as a result of better prevention of colorectal cancer, the risk of these clinical problems will further increase.We present a clinical overview of extra-intestinal manifestations, including management and treatment options for the FAP syndrome. Furthermore, we provide recommendations for surveillance of FAP complications based on available literature.

Key Words: Familial adenomatous polyposis—Extra-intestinal manifestations—Multisystem disorder.

In the early 1950s, Gardner described that in some patients hereditary polyposis could occur simultaneously with multiple cutaneous and subcutaneous lesions and osteomatosis.[1] Initially, the triad of extra-intestinal manifestations composed of soft tissue cysts, osteomas and dental abnormalities was referred to as Gardner syndrome. This terminology is now used only from a historical point of view. Indeed, retrospective research proved that extra-intestinal tumors could be found in almost all families with familial adenomatous polyposis (FAP), if the affected

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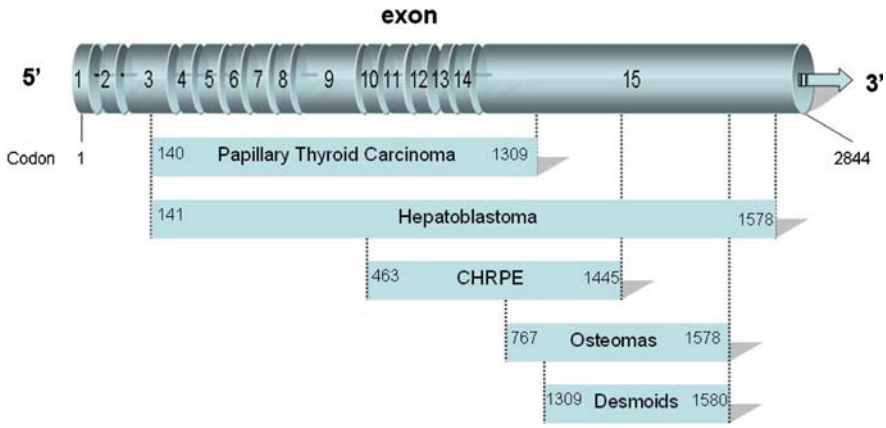

FIG. 1. Genotype–phenotype correlations of extra-intestinal familial adenomatous polyposis (FAP) manifestations according to the available literature.[21,39,109,111] The APC gene consists of 15 exons. The highest cumulative frequencies of extra-colonic manifestations are found between codons 976–1,067 and 1,310–2,011. The margins of codon regions associated with extra-intestinal manifestations are not absolute and merely provide a guideline. No genotype–phenotype correlations have been established for pancreatic carcinoma, brain tumors or adrenal gland adenomas. *CHRPE* congenital hypertrophy of the retinal pigment epithelium.

patients were examined carefully.[2] FAP is not uncommon with an incidence reported to vary from 1:6,850 to 1:23,700 live births[3–5] and leads to development of colorectal carcinoma in almost 100% of cases by 40 years of age. The introduction and work of (national) polyposis registries and prophylactic colectomy has greatly improved life expectancy for patients with FAP.[6,7]

Surveillance recommendations for the prevention of other intestinal malignancies, such as duodenal ampullary carcinomas and gastric carcinomas, have been issued and are widely implemented.[8–11] In contrast, less attention has been given to the diverse extra-intestinal features of FAP. Clinical awareness of health problems that are (seemingly) not related to intestinal manifestations is necessary because improved life expectancy in FAP patients has increased their prevalence.

In this paper, we review the extra-intestinal manifestations of FAP. To facilitate risk assessment of identified adenomatous polyposis coli (APC) gene mutations, a guideline of well-established genotype–phenotype correlations is provided (Fig. 1). In addition, recommendations for surveillance are given for extra-intestinal malignancies (Table 1) and benign manifestations (Table 2). The commonly used GRADE criteria were used to describe both the strength of recommendations (1–4) and the quality of evidence (A–D).

MOLECULAR GENETICS

The APC gene located on 5q21–22 is mutated in FAP. Most mutations will result in stop codons and lead to truncation of the APC gene product. These mutations have a nearly complete penetrance of the colonic phenotype, but a variable penetrance of extra-colonic manifestations of the disease. Modifier genes, variable interference of different mutant APC proteins on the wild-type APC function and environmental factors may play a role in extra-intestinal tumor formation.[12]

The APC protein is a large scaffolding protein with several functions.[13] It is involved in the Wnt signaling cascade. As part of a multiprotein complex, the APC protein downregulates β-catenin activity.[14] In the absence of a Wnt signal, APC forms a complex with the protein β-catenin, allowing it to be targeted for destruction. When APC function is lost, β-catenin accumulates in the cytoplasm and binds to several transcription factors of the TCF/LEF, thereby altering the expression of various genes affecting proliferation, differentiation, migration and apoptosis of cells.[13] In addition, APC stabilizes microtubules, leading to chromosomal stability.[15,16] Inactivation of APC can lead to defective chromosome segregation and aberrant mitosis.[17]

FAP AND THYROID CARCINOMA

Epidemiology and Genetics

Thyroid cancer in a patient with FAP was first described in 1949 by Crail.[18] Almost 40 years later, Plail and coworkers reviewed 998 patients with FAP and found that thyroid carcinoma occurred more frequent in FAP patients than in the general popu-

TABLE 1. *Recommendations for surveillance of malignant extra-intestinal manifestations of familial adenomatous polyposis*

Manifestation	Population at risk[a]	Lifetime prevalence	Recommendation for surveillance	Additional diagnostic considerations
Papillary thyroid carcinoma	Women, 15–35 years Concomitant CHRPE Family history of thyroid carcinoma	1–2%	Look for palpable nodules at least yearly and refer to endocrinologist for FNAB if present *Level 3, B: Sigurdson*[26]	Optionally: perform ultrasonography of thyroid gland every 1–2 years and refer if nodules present are larger than 10 mm or larger than 5 mm with characteristics associated with malignancy[b] *Level 3, B: Papini*[29]
Hepatoblastoma	Boys, 0–4 years, but may present up to 16 years Family history of hepatoblastoma	1–2%	Serial measurement of aFP Abdominal ultrasound Suspicious hepatic lesions: CT or MRI Surveillance should commence within the first month after birth and continued every 3 months at least up to the age of 4 years[38] *Level 4, D:* Thomas,[36] Aretz,[38] Sanders[43]	
Brain tumor	Medulloblastoma: 5–38 years Other brain tumors: 22–80 years Family history of brain tumor	1–2%	Surveillance not recommended *Level 4, D: this article*	Awareness of signs and symptoms related to CNS tumors
Pancreatic cancer	$> \pm 30$ years	1%	Surveillance not recommended *Level 4, D: this article*	Awareness of signs and symptoms related to pancreatic cancer Pay attention to the pancreas at CT or MRI

CHRPE congenital hypertrophy of the retinal pigment epithelium, *FNAB* fine needle aspiration biopsy.
[a] Supplementary to those defined by codon mutation (as depicted in Fig. 1).
[b] Hypoechogenic nodules, irregular margins, hypervascularity or microcalcifications.

lation.[19] The largest FAP registries have reported a life time risk of 1–2%,[19,20] but some consider this an underestimation.[21] There is a striking female preponderance (female to male ratio 17:1). The average age at diagnosis is 27 years. It has never been found to present before 15 years of age.[22] Young women (less than 35 years of age) are at particular risk of developing thyroid cancer, and their chances of being affected are approximately 160 times that of normal individuals.[19] Familial clustering has been described several times.[23] A strong association with Congenital Hyperplasia of the Retinal Pigment Epithelium (CHRPE, see below) exists—since most of the mutations cluster in the genomic area, characteristic of both extra-colonic manifestations. Genetic analysis most often shows a mutation in exon 15, in the 5' portion of the APC gene outside the Mutational Cluster Region (i.e., before codon 1,220).

Clinical Findings

Papillary thyroid carcinoma (PTC) almost invariably presents as a node in the thyroid gland. Other thyroid carcinomas have been described but are very rare. Fine needle aspiration biopsy (FNAB) of the node will establish the diagnosis, but sometimes a diagnostic hemithyroidectomy is necessary. The histological pattern typically shows a cribriform (morular) papillary thyroid carcinoma, but this is not entirely specific. Although multifocality in the thyroid gland and regional lymph node involvement often occur, FAP-associated PTC is a relatively indolent tumor. Treatment of PTC initially consists of total thyroidectomy and administration of radioiodine (131-I), followed by TSH suppression therapy. As a group, the prognosis is very favorable, with recurrence-free patient survival of more than 15 years.[21,23] After proper treatment, patients with no distant metastases are likely to have a normal residual lifespan.[24,25]

Considerations for Surveillance

Thyroid surveillance in patients with FAP syndrome is recommended due to the known increased risk of thyroid cancer in this group and the ease and

TABLE 2. *Recommendations for surveillance of benign extra-intestinal manifestation of familial adenomatous polyposis*

Manifestation	Population at risk[a]	Lifetime prevalence	Recommendation for surveillance	Additional diagnostic considerations
Adrenal tumors	>14 years	7–13%	Surveillance not recommended Refer to endocrinologist if adrenal adenoma is present at CT or MRI *Level 4, D this article*	Adrenal adenomas can produce cortisol, aldosterone, androgens or catecholamines Pay attention to signs or symptoms related to excess of these hormones (e.g., moon-face, striae, hypertension, hirsutism) *Diagnostic work-up according to NIH Guideline* [81]
Desmoid tumors	Peak incidence ± 30 years After surgery (median time ± 2 years) Family history of desmoid tumors Presence of osteomas	20%	Surveillance not recommended *Level 4, D: this article*	Evaluate palpable abdominal masses or symptoms related to abdominal organ obstruction Optionally: consider CT or MRI scan *Level 3, C: Healy*[95]
Osteomas	Presence of CHRPE or desmoids Positive family history of osteomas	20%	Surveillance not recommended *Level 4, D this article*	Pay attention to mandibula problems. Refer to dental surgeon if osteomas cause problems. Various bone localizations are possible
Dental abnormalities	Children/during dental development	17%	Refer to dentist or dental surgeon Serial OPG every 1–2 years *Level 4, D: Wijn,*[101] *this article*	

CHRPE congenital hypertrophy of the retinal pigment epithelium, *OPG* orthopantomography (panorex).
[a] Supplementary to those defined by codon mutation (as depicted in Fig. 1).

simplicity of the surveillance program. Recommendations are comparable to those for populations at high-risk of thyroid cancer, such as childhood cancer survivors who received radiotherapy to the head, neck or upper region.[26] Although no specific protocols are available, physical examination of the neck and thyroid gland can be advocated.[26] FNA—in case of suspected nodules—is recommended.[27,28] The use of (color Doppler) ultrasonography for thyroid gland examination is still controversial, but makes it possible to analyze non-palpable thyroid nodules and assess potentially malignant characteristics.[29]

FAP AND HEPATOBLASTOMAS

Epidemiology and Genetics

Hepatoblastoma is an embryonal neoplasm composed of malignant epithelial tissue with variable differentiation, most often with embryonal or fetal components. The tumor predominantly occurs in children between 6 months and 3 years of age, but the age at diagnosis can range from prenatal stages to 16 years. The clinical association between hepatoblastoma and FAP was first reported by Kingston et al. in 1983,[30] and more than 50 cases have now been reported.[31] However, hepatoblastomas are also related to several other genetic abnormalities and malformation syndromes, the most important of which are Beckwith-Wiedemann syndrome, trisomy 18, fetal alcohol syndrome and extreme premature birth.[32] The risk of hepatoblastoma is 750–7,500 times higher in children from FAP families than in the general population.[33,34] This higher incidence contributed significantly to the observed increased cancer mortality in the age group between 1 and 4 years in a Japanese polyposis registry;[35] however, the absolute risk for hepatoblastoma in children with FAP is less than 2%.[33] Familial clustering of hepatoblastomas has been described several times (reviewed by Thomas et al.[36]). The age at diagnosis and the increased incidence in boys is similar between FAP- and non-FAP-related hepatoblastomas.[37] Mutation analysis revealed that almost 95% of the mutations were on the 5' to mid region of the APC gene between codons 141 and 1,751.[37,38] However, it is generally accepted that the site of the APC mutation cannot be used to predict the occurrence of hepatoblastoma.[39] Because FAP and hepatoblastoma are rare, the precise epidemiological relationship between these diseases has been difficult to quantify.

Clinical Findings

Hepatoblastoma presents as an abdominal mass. While often asymptomatic in early stages, patients typically present with constipation, abdominal pain,

vomiting, weight loss, anemia and thrombocytosis in advanced tumors. The diagnosis is confirmed by an elevated α-fetoprotein (αFP) in approximately 90% of cases, by liver imaging and, ultimately, by biopsy.[40] Survival is highly related to the success of complete tumor resection.[38] Preoperative chemotherapy (usually consisting of cisplatin and doxorubicin) is very helpful and many previously irresectable tumors can become completely amenable to surgery. Although the combination of chemotherapy and surgery is very successful, an estimated 25% of all patients do not survive this disease.[38,41]

Considerations for Surveillance

There are no validated and generally accepted guidelines of surveillance for hepatoblastoma in FAP families. According to their recently published surveillance protocol, Aretz et al. recommend analysis of (changes in) serial αFP measurements and abdominal ultrasound. Suspicious hepatic lesions on sonography should be further investigated with CT or MRI. Surveillance should commence within the first month after birth and continued every 3 months at least up to the age of 4 years.[38] Due to limitations in the interpretation of αFP as a marker for hepatoblastoma at a very young age or due to the lack of αFP production in undifferentiated tumors, false-positive or false-negative results can be obtained. When the classical criteria of Wilson and Jungner are applied for surveillance, it remains questionable whether the diagnostic tests are suitable.[42] However, the disease is more easily curable if detected at an early stage, and several authors thus favor surveillance of young children in FAP families.[36,38,43]

FAP AND BRAIN TUMORS

Epidemiology and Genetics

In 1959, Turcot and colleagues described two teenaged siblings with numerous adenomatous polyps of the colorectum in whom malignant tumors of the central nervous system (CNS) developed.[44] The association of primary brain tumors and colorectal polyposis has since been described in the literature under the eponym "Turcot's syndrome". The association between brain tumors and colorectal polyposis has been renamed the "brain tumor–polyposis" (BTP) syndrome.[45] Both clinically[45] and molecularly,[46] this appeared to be a heterogeneous disorder with at least two clinical entities. The BTP syndrome type 1 results from mutations in DNA mismatch repair genes characteristic of Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC). The brain tumors are usually high-grade astrocytomas or glioblastomas.[45] It is also referred to as "true Turcot's syndrome". It should be noted that the original description of Turcot is confusing, because what he described was most likely a HNPCC case with (few) colon polyps. The BTP syndrome type 2 typically consists of a medulloblastoma associated with colorectal polyposis in a patient who belongs to a FAP family.[45] In the context of this review, we have focused on FAP-associated brain tumors. The terminology of BTP or Turcot's syndrome is preferentially used only from a historical point of view.

Medulloblastomas account for 80% of the brain tumors found in FAP. However, high-grade astrocytomas and ependymomas have also been described.[46] Medulloblastoma is a highly malignant embryonal CNS tumor primarily affecting children in the first decade of life, and 70% occurs before the age of 16 years. The relative lifetime risk of any brain tumor among members from a FAP family is increased by a factor 7, and that of medulloblastoma by a factor 90. However, the absolute lifetime risk of any brain tumor is approximately 1–2%.[46]

Clinical Findings

Medulloblastoma generally occurs in the midline cerebellum and, therefore, presents with signs or symptoms of obstructive hydrocephalus and cerebellar dysfunction, usually over a period of weeks to months. Typical symptoms are emesis, horizontal diplopia, clumsiness or frank ataxia, and headaches. Currently, patients with medulloblastoma are best treated with surgical removal of the tumor, radiation therapy and/or chemotherapy depending on age, extent of resection and presence of metastases.[47] The overall 5-year survival has risen to 50–70% in the past decades. The median overall survival appeared to be much longer among patients who present with colon polyps first.[48] This observation has to be confirmed in other series of patients.

Considerations for Surveillance

There are a number of familial syndromes that predispose individuals to CNS tumors; examples are von Hippel-Lindau (VHL) disease and neurofibromatosis type 1 (NF-1). The lifetime risk of CNS hemangioblastomas in VHL is 60–80%. Improved surveillance of patients at risk for VHL disease,

including yearly MRI of the craniospinal axis from the age of 11 years, has substantially improved diagnosis and treatment.[49] Optic nerve gliomas are seen in 15% of patients with NF-1. Patients with NF-1 are usually seen by a multidisciplinary clinical team. Cranial MRIs for the detection of these gliomas are usually reserved for children with abnormalities during their annual vision evaluation.[50] In contrast to these familial syndromes, brain tumors in FAP families are associated with a much lower lifetime risk. Furthermore, annual surveillance of asymptomatic patients may not be often enough, since medulloblastoma is a highly malignant tumor that is usually only symptomatic 6 months or less before diagnosis. Therefore, surveillance by means of regular CT or MRI cannot be advocated. However, members from a FAP family who do not yet have polyposis, but do have signs or symptoms suggestive of a brain tumor, should be evaluated with neuro-imaging because brain tumors present before the diagnosis of polyposis in over half of the FAP patients.[46] Careful evaluation is also important among FAP families in which one member already has a brain tumor since familial clustering occurs. Of such families with FAP-associated brain tumors, 40% had two affected members.[46] Doctors who care for members of FAP families should be aware of the association with medulloblastoma and, thus, increase their sensitivity to signs or symptoms of CNS tumors. Additionally, education of members of FAP families about extracolonic manifestations could be useful.

FAP AND PANCREATIC TUMORS

Epidemiology and Genetics

Pancreatic tumors in FAP patients are rare. In a cohort study of 1,391 patients with FAP reported in the Johns Hopkins Registry, 4 patients were found to have developed a pancreatic adenocarcinoma.[51] Their age ranged from 32 to 78 years. From this, a significantly higher relative risk [RR: 4.5 (95% confidence limits 1.2–11.4)] of pancreatic carcinoma was calculated in polyposis patients and their relatives than in the general population. Few other types of pancreatic malignancies have been described. Two cases of intraductal papillary-mucinous neoplasm,[52,53] one cystic and papillary carcinoma,[54] one acinar cell carcinoma[55] and two islet cell tumors[56,57] have been reported in association with FAP. In addition, some pancreatic premalignant lesions[58–60] and a pancreatic cyst due to desmoid fibromatosis in a 17-year-old male[61] have been described. No evidence of familial clustering is evident from the literature.

Clinical Findings

Pancreatic carcinomas are often clinically silent for a long time. In more advanced stages, patients may experience pain, weight loss, jaundice or diarrhea (steatorrhea). Diabetes, pancreatitis and thrombophlebitis also occur. The prognosis of adenocarcinomas of the pancreas is generally poor. Treatment options consist of surgery and chemotherapy.[62]

Considerations for Surveillance

In view of the low prevalence of pancreatic cancer and the scarcity of published data, surveillance is not routinely recommended. Future protocols may include MR imaging and endoscopic ultrasonography (EUS).[63] The clinician should be aware that pancreatic neoplasia can develop. When abdominal imaging is performed, for example in the evaluation of desmoid tumors or adrenal gland adenomas, attention should be given to potential abnormalities in the pancreas.

FAP AND ADRENAL TUMORS

Epidemiology and Genetics

Adrenal adenomas are frequently occurring extra-intestinal manifestations of FAP. The first case of a FAP patient with an adrenal adenoma was published almost a century ago.[64] Since then, approximately 50 cases have been reported in the literature, many of them being asymptomatic and discovered at autopsy.[65–76] Age ranges from 14 to 70 years, with a median of approximately 40–50 years. As a result of technological advances in imaging techniques such as CT and MRI during the last decades, new information has become available regarding the prevalence of adrenal masses in both the general population and patients with FAP. In a retrospective study, Marchesa et al. found a 7% prevalence of so-called ''incidentalomas'' in FAP patients,[69] compared with approximately 3% in the general population.[77] Smith et al. even showed a prevalence of adrenal masses of 13% in a prospective study.[74] Familial clustering has also been described.[71] Although the prevalence of adrenal masses in FAP patients are two to four times as high as in the general population, the clinical presentation, and biological behavior do not seem to be different.[69,74]

Most adrenal adenomas do not produce hormones, although production of cortisol,[66,69,76] aldosterone[65] and their combination have been reported.[73] Smith et al. described a patient with a pheochromocytoma.[74] Data on genetic analysis are limited, and only three mutations have been described (codons 1,061, 1,542 and 1,981). The latter was associated with multiple and bilateral adenomas.[68] Adrenal carcinomas in association with FAP are very rare and only six have been described.[69,70,72,78–80]

Clinical Findings

Adrenal adenomas usually present as clinically unapparent adrenal masses, detected incidentally with imaging studies conducted for other reasons. The two major clinical concerns are that adrenal masses may overproduce hormones or that they represent adrenal cortical carcinomas. By definition, no clinical symptoms or signs of adrenal disease should be present at the time of diagnosis in patients with incidentally detected adrenal masses. However, a more detailed questioning and a careful physical examination might reveal subtle evidence for hormone excess. Hormonal assessment is usually done by an endocrinologist, in some countries also by an endocrine surgeon. In addition, repeat imaging after 6–12 months is necessary to assess malignant potential. Clinically silent lesions that are less than 4 cm are generally not resected. Surgery is indicated in adrenal masses larger than 6 cm because they frequently harbor malignancies and, in the case of hormone-producing adenomas, because of the metabolic consequences. For lesions between 4 and 6 cm, with benign characteristics on imaging, that do not appear to overproduce hormones, both close follow-up and adrenalectomy are considered a reasonable approach.[81]

Considerations for Surveillance

Based on the low incidence of hormone-producing adrenal adenomas and the rarity of adrenal cancer in FAP patients, surveillance does not seem to be justified. However, clinical awareness is very important. Subtle clues such as weight gain, hypertension or hypokalemia and diabetes mellitus may prompt further hormonal analysis. Once a tumor in the adrenals is identified, hormonal and radiological evaluations according to the NIH conference guidelines need to be performed.[81] Patients should be referred to an endocrinologist. This is especially important since recent reports suggest that up to 20% of patients with adrenal incidentaloma (which means 1–3% of all FAP patients) have some form of subtle and subclinical hormonal dysfunction resulting in an increased risk of metabolic disorders and cardiovascular disease.

FAP AND DESMOID TUMORS

Epidemiology and Genetics

Desmoid tumors are a very important cause of mortality in patients with FAP.[6] There is an approximate 1000-fold increase of developing desmoid tumors in FAP patients when compared to the general population.[82] Desmoids can be found at any age and have been documented from infancy to 81 years of age.[83] The most common age of presentation is between 20 and 40 years, with a median age of 30 years, as reviewed by Knudsen et al.[84] The risk of such tumor formation is increased after prior surgery. Jarvinen found that the median interval between the operation and the diagnosis of desmoid was a little over 2 years.[85] The lifetime risk associated with these tumors in a Finnish and Italian registry was estimated to be approximately 21%.[86,87] The most important risk factors are a positive family history, presence of osteomas or epidermoid cysts and an APC gene mutation between codons 1,444 and 1,578.[86]

Clinical Findings

Most desmoid tumors in FAP patients arise in the abdomen, most frequently intra-abdominally (in the mesentery of the small bowel) but also in the abdominal wall (some in surgical scars). Fewer than 10% are located outside the abdomen.[83,88,89] Depending on localization, desmoid tumors can be either asymptomatic or cause pain and various gastrointestinal complaints. Mesenteric desmoids may cause small bowel obstruction, ureter compression, small intestinal ischemia, abscess formation, intestinal perforation or fistulas.

Desmoid tumors are poorly understood. They are infiltrative and non-metastasizing, with a histologically benign appearance apart from the surrounding tissue infiltration. Approximately 5–10% appear to resolve spontaneously.[88,90] In addition, 30% undergo cycles of progression and resolution, and 50% remain stable after diagnosis. However, 10% progress rapidly, growing to massive sizes and infiltrating adjacent structures.[90] Treatment is indicated when they cause symptoms, pose a great risk to adjacent struc-

tures or create cosmetic concerns. There are no controlled trials on the treatment of desmoid tumors. Furthermore, many studies of desmoids are confounded by inclusion of both FAP-associated and sporadic disease, which may represent two biologically distinct entities.[91] Thus, treatment modalities are not well established. For intra-abdominally located tumors, treatment with sulindac (non-steroidal anti-inflammatory drug) and/or a selective estrogen receptor modulator (tamoxifen/torimifene) is advised as first line therapy.[83,84,89] Cytotoxic chemotherapy has been used for desmoids that are not responsive to less aggressive therapies.[61,83,84] Surgery is generally not recommended as first-line therapy for intra-abdominal desmoids because recurrence rate and morbidity are reported to be extremely high, including bleeding, short bowel and postoperative death (8 of 22 patients in the series from St. Marks),[88] although a later report from the same group claimed that it was less hazardous than previously reported.[92] In addition, it is commonly believed that resection triggers growth and therefore recurrences. However, when medical treatment of large mesenteric desmoids fails, surgery remains a valuable option.[93]

Surgery is indicated as first line therapy for tumors located in the abdominal wall and extra-abdominally.[88] For patients with positive resection margins, adjuvant radiotherapy can be given.[94] Nevertheless, it can be argued that abdominal wall desmoids need not be resected, but can be observed as the natural history is variable and recurrence after surgery is frequent.

Considerations for Surveillance

There is no consensus about surveillance of patients with FAP with regard to the presence of desmoid tumors, principally because there are no real preventive strategies. Thus, some advocate no surveillance at all. However, because the mortality due to polyposis is decreasing and morbidity and mortality from desmoid tumors is increasing, it seems reasonable to look for intra-abdominally located desmoid tumors using CT or MRI scan,[95] especially in patients with a gene mutation between codons 1,444 and 1,578 or in those with a family history of desmoids. Because desmoids often arise as a consequence of tissue trauma, a delay of surgery and the type of surgery should be considered in patients at high risk of developing desmoids, at least in those with a smaller number of polyps or when the onset of colon malignancies is expected to occur later in life. Mutation analysis may be of help in such cases as an aid in decision making.[96–99] Ileal pouch–anal anastomosis is advocated as the appropriate type of surgery in FAP patients with a positive family history of desmoids.[100]

FAP, OSTEOMAS AND DENTAL ABNORMALITIES

Epidemiology and Genetics

The prevalence of osteomas is about 20% in FAP patients compared with 1–2% in the general population. Mutations are found in codons 767 to 1,578. Dental abnormalities occur frequently with an estimated prevalence of 17%.[101] As with other manifestations, osteomas and dental abnormalities may also precede the actual development of colon polyps in FAP patients.[102]

Clinical Findings

Osteomas are benign bone growths most commonly found in the skull and mandible. However, they may occur in any bone of the body.[103] Their size ranges from less than a millimeter to several centimeters. They can give rise to cosmetic concerns.

The dentition during childhood can be disturbed by the presence of supernumerary teeth, dentigerous cysts and a phenomenon referred to as secondary retention of teeth. Supernumerary teeth and dentigerous cysts can obstruct normal teeth from erupting. This is often an indication for surgical removal. Supernumerary teeth are usually present before the age of 10 years. The development of cysts can occur at any age. Dentigerous cysts are those that develop from the epithelium of the enamel organ; therefore, the risk of developing such a cyst is greatest when teeth are still developing in the jaw. They can sometimes grow and occupy more than a quarter of the mandible. Such cysts lead to local destruction of the jaw and removal can have profound consequences for the patient. The phenomenon of secondary retention of teeth has also been described in FAP patients. In such cases, erupted teeth are retained at a certain position in the jaw, which is usually caused by ankylosis. This results in a submerged position of the involved tooth. It is not necessary to treat such teeth when they do not obstruct the eruption of other teeth. When these teeth give problems, removal is usually the only option.

Considerations for Surveillance

A normal dentition is fully developed at 18 years of age. Disclosure at an early stage is therefore important

in reducing the morbidity associated with surgical removal. The literature on dental anomalies in FAP patients is mainly restricted to a description of the pathology,[104] and no surveillance recommendations have been published. In comparable syndromes with a high risk of developing cysts in the jaws, such as the nevoid basal cell carcinoma syndrome, it is recommended that a routine panorex is made every 1–2 years for early disclosure of cysts.[105] The incidence of the development of dental anomalies in FAP is clearly increased relative to that in normal individuals, and treatment at a later age has been described as complicated.[106] It is therefore recommended that in the routine follow-up, a panorex is included at least every 2 years in a developing child until the teeth have erupted ($\sim$ 18 years).[101] In this way, problems caused by undetected dental abnormalities later in life can be prevented.

FAP AND OTHER BENIGN MANIFESTATIONS

Epidermoid cysts, fibromas and lipomas are all considered (sub)cutaneous lesions and may cause cosmetic problems. Cysts occasionally become infected, necessitating operative removal. Nasopharyngeal angiofibromas have been described in some patients with FAP syndrome. They occur 25 times more frequently in patients with FAP than in an age-matched population.[107]

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is the most common extra-colonic manifestation of FAP and an early marker for it. Approximately 60% of patients with FAP have CHRPE. Multiple or bilateral patches of these lesions are highly specific (95%) for FAP syndrome.[108] It appears as well-demarcated grey-brown to black round or oval lesions in the retinae of affected individuals and is not known to cause any clinical problems. Mutations in the region between codons 543 and 1,309 in the APC gene are associated with a high risk of CHRPE.[109] Ophthalmoscopic surveillance for CHRPE is a direct, non-invasive and inexpensive test. If the index case has CHRPE, then surveillance for CHRPE has been successfully used as an early clinical marker to detect affected family members.[110]

CONCLUSION

FAP is due to a germline mutation in the APC gene. The development of colorectal cancer stands out as the most characteristic manifestation of this disease. Prophylactic colectomy has improved the life expectancy of patients, as a result of which the prevalence of other manifestations has increased. In appreciation of the development of various forms of benign and malignant tumors, it seems more appropriate to speak of FAP syndrome. The diverse multisystem effects of FAP syndrome manifest during different phases of life and in association with different mutations. Some tumors can present during early childhood before the classical colonic polyps cause problems, and this may be the first clue that FAP is present. Many FAP cases are due to spontaneous mutations, with no antecedent family history, and many parents are poorly informed about their own FAP and cannot be counted on to connect their child's disease (for instance a hepatoblastoma or a brain tumor) with their own. Therefore, to optimize health care for FAP families, the surgeon and the gastroenterologist who are often the primary FAP experts also have a key role as education providers.

SEARCH STRATEGY

We searched the PubMed database using the keywords Familial Adenomatous Polyposis or Gardner syndrome, combined with the terms molecular genetics, thyroid carcinoma, hepatoblastoma, brain tumor, pancreatic tumor, adrenal tumor, desmoid tumor, osteoma, dental abnormalities or benign manifestations. We focused mainly on manuscripts published during the past 10 years, but have also referenced key papers from before then. In addition, relevant articles that were identified by papers found in this search strategy have also been referenced.

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