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The natural history of familial adenomatous polyposis syndrome: A 24 year review of a single center experience in screening, diagnosis, and outcomes

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ABSTRACT

Purpose: Understanding the natural history of Familial Adenomatous Polyposis (FAP) will guide screening and aid clinical management.

Methods: Patients with FAP, age ≤20 years presenting between 1987 and 2011, were reviewed for presentation, diagnosis, extraintestinal manifestations, polyp burden, family history, histology, gene mutation, surgical intervention, and outcome.

Results: One hundred sixty-three FAP patients were identified. Diagnosis was made by colonoscopy (69%) or genetic screening (25%) at mean age of 12.5 years. Most children (58%) were asymptomatic and diagnosed via screening due to family history. Rectal bleeding was the most common (37%) symptom prompting evaluation. Colon polyps appeared by mean age of 13.4 years with >50 polyps at the time of diagnosis in 60%. Cancer was found in 1 colonoscopy biopsy and 5 colectomy specimens. Family history of FAP was known in 85%. 53% had genetic testing, which confirmed APC mutation in 88%. Extraintestinal manifestations included congenital hypertrophy of the retinal pigment epithelium (11.3%), desmoids (10.6%), osteomas (6.7%), epidermal cysts (5.5%), extranumerary teeth (3.7%), papillary thyroid cancer (3.1%), and hepatoblastoma (2.5%). Six patients died secondary to FAP.

Conclusions: Clinical presentation and manifestations in pediatric FAP are variable. We suggest an individualized patient-oriented screening algorithm that allows for earlier screening and appropriate management.

Familial adenomatous polyposis (FAP) is an autosomal dominant polyposis syndrome classically characterized by mutation in the APC gene on the long arm of chromosome 5 [1]. This results in formation of hundreds to thousands of adenomatous polyps in the colon and rectum early in life. Progression to colorectal cancer occurs with nearly complete penetrance by age 40–50 years; however, malignancy in childhood does occur [2]. Patients with FAP may also develop upper gastrointestinal polyps, although these less commonly progress to malignancy as compared to colon and rectal adenomas [3–5]. Sites other than the gastrointestinal tract are at increased risk of tumors and malignancy including: thyroid, liver, brain, bone, adrenal gland, retinal pigment, and subcutaneous tissues.

Due to the increased risk of malignancy, screening protocols have been suggested [6–8]. In general, guidelines recommend sigmoidoscopy every 2 years beginning at age 10 to 12 years to evaluate for the presence of adenomatous polyps. Once an adenoma is identified, annual colonoscopy is recommended. One study [7], suggests that a more individualized approach may be required due to phenotypic/genotypic variability.

The goal of this study was to better understand the natural history of these FAP-associated phenomena, which could facilitate the rational selection of interventions and best practices for comprehensive screening to reduce the risk of malignancy in these unique patients.

1. Materials and methods

This study was approved by our institutional review board. All patients aged ≤20 years presenting to our institution between 1987 and 2011, with a diagnosis of FAP were included. A multi-disciplinary group including gastroenterologists, medical geneticists, surgeons, endocrinologists, dermatologist, radiologists, pathologists, and social work assists in the care of these patients and families. Patient medical records were retrospectively reviewed for demographics, method of FAP diagnosis, presenting symptoms and family history.

Development and extent of upper gastrointestinal polyps and colorectal polyps were abstracted from endoscopy reports. Since endoscopists varied across the years, the polyp burden as described in the report was arbitrarily set at: 1–20 polyps, 21 to 50 polyps, and greater than 50. Polyp size (in mm) was also noted where available.

Presence of extraintestinal manifestations was recorded, including congenital hypertrophy of the retinal epithelium (CHRPE), desmoid tumors, epidermal cysts, osteomas, hepatoblastoma, thyroid cancer,

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dental anomalies and brain tumors. Long term outcomes were tracked until last documented follow-up.

Diagnosis of FAP was confirmed by a positive genetic test in recent patients, or by clinical presentation with pathology confirmation in older cases. Pathology reports were reviewed to confirm presence of adenomatous polyps in all patients.

2. Results

2.1. Diagnosis

Over the 24 year study period, 163 patients ≤20 years of age were treated at our institution with a confirmed diagnosis of familial adenomatous polyposis (Table 1). Gender distribution was essentially equal, with 76 (46%) males and 87 (54%) females. Diagnosis of FAP was confirmed at a mean age of 12.5 years (range 0.5 to 20 years, median 13 years). Initial evaluation for FAP was prompted most frequently by a positive family history of FAP (n = 92, 56%). The remainder of patients came to a diagnosis of FAP after evaluation for new onset symptoms (Table 2). Median follow-up was 5.0 years (mean 6.4, range 0 to 25 years).

Diagnosis of FAP was most frequently made by colonoscopy (n = 111, 69%) or genetic screening (n = 40, 25%). However, the diagnosis was also made by barium enema (n = 6, 3.7%) in select cases early in the study period, and on occasion by the presence of extraintestinal manifestations (n = 3, 1.8%).

2.2. Endoscopy

Colonoscopy data were available for 112 patients. Colon polyps were documented via endoscopy by mean age of 13.4 (median 13.5 years), but were observed as young as 8 months. Seventeen patients (15%) younger than 7 years of age and 41 patients (37%) younger than 10 years of age were found to have adenomatous polyps on endoscopy. Polyp burden exceeded 50 polyps at the time of diagnosis in 60% of cases and most frequently showed pancolonic distribution (Table 3). Polyp size ranged from 1 mm to 40 mm, with a median size of 5 mm at initial endoscopic evaluation. Pathology from endoscopic biopsies and polypectomies specimens was available for 101 cases. Most frequently, specimens were involved by low grade dysplasia (n = 87, 86%). Twelve cases were without dysplasia (benign), however 1 patient had high grade dysplasia (age 18 years) and another patient (age 18 years) had invasive cancer at the time of initial endoscopic documentation of colon polyps.

Table 1
Demographics.

	n	Mean	Range
Gender			
Male	76	46%	
Female	87	54%	
Family History			
Known FAP in family	137	84%	
Sporadic	26	16%	
Age (years)			
Initial diagnosis	162	12.5	0.5-20
*Familial cases**	136	12.1	0.5-20
*Sporadic cases**	26	14.7	1.5-20
Colon polyp onset	146	13.3	0.5-20
*Familial cases***	123	12.9	0.5-20
*Sporadic cases***	23	15.2	4-20
Upper GI polyp onset	96	17.4	7-37
*Familial cases****	76	17.1	7-37
*Sporadic cases****	20	18.4	11-36
Colectomy	127	15.4	4-24

* p-value = 0.01.
** p-value = 0.02.
*** p-value = 0.29.

Table 2
Initial Indication for FAP evaluation.

Presenting Symptom	n (%)
Family History of FAP	92 (56.4)
Hematochezia	28 (17.2)
Diarrhea	13 (8.0)
Abdominal Pain	11 (6.7)
Extraintestinal Manifestation	10 (6.1)
Unknown	4 (2.5)

Upper gastrointestinal (UGI) polyps were documented via upper endoscopy in 96 patients (58.9%) with mean age of diagnosis at 17 years (range 7 to 37 years). The stomach had polyps in 84 patients (51.5%) and duodenal polyps were found in 55 patients (33.7%). Pathology revealed benign polyps in 31 patients (32.3%) and low grade dysplasia in 42 patients (43.8%). No high grade dysplasia or invasive cancer was identified upon initial diagnosis of UGI polyps. One patient developed extensive progression of duodenal polyposis with high grade dysplasia ultimately requiring pancreaticoduodenectomy at age 44.

2.3. Genetics

There was a known family history of FAP in 137 patients (84%). Where available (n = 74), age of onset of colon polyps in family members was compared to our study patients. Colon polyps appeared within 2 years of the age when family members developed colon polyps in 13.5% of cases, within 5 years in 25.7 %, and within 10 years in 40.5% Medical records did not specify whether polyp burden followed a familial pattern although anecdotal cases tended to confirm the familial aggregation of a particular presentation. Genetic testing was performed in 87 patients (53%) and became more frequent in recent years. Gene tests confirmed APC mutation in 78 patients (90%) and unknown mutations in the remainder (genetic testing was performed elsewhere). Per family and patient preference, genetic testing was performed at a variety of ages (range: infant to 20 years). All patients who underwent genetic testing were seen by a genetic councilor to provide appropriate education and follow-up.

2.4. Surgery

Colectomy has been performed for 124 patients (76%) at a mean age of 15.4 years, with our youngest colectomy at 4 years of age. Ileal pouch anal anastomosis was performed in 103 patients and is our preferred practice. The anal anastomosis was performed with a mucosectomy and hand sewn anastomosis in 88% of cases, and the remaining 12% were stapled anastomoses. Select other procedures were performed, including ileorectostomy (13 patients), end ileostomy (7 patients), and straight ileoanal anastomosis (1 patient). Surgical pathology revealed benign polyps in 2 patients, low grade dysplasia in 99 patients, high grade dysplasia in 5 patients (ages 13,

Table 3
Colon polyposis features.

Feature	n (%)
Polyp Burden	
1 to 20 polyps	30 (26.8)
21 to 50 polyps	13 (11.6)
>50 polyps	69 (61.6)
Polyp Distribution	
Right Colon	4 (3.7)
Left Colon	15 (14.0)
Rectum	1 (0.9)
Pancolonic	87 (81.3)

16, 17 and two 20 year olds) and invasive cancer in 5 patients (ages: one at 19 years, two at 18 years, and two at 17 years of age).

2.5. Extraintestinal manifestations

Extraintestinal manifestations included congenital hypertrophy of the retinal pigment epithelium, desmoids, osteomas, epidermal cysts, extranumerary teeth, papillary thyroid cancer and hepatoblastoma. Incidence of extraintestinal manifestations is described in Table 4.

Papillary thyroid cancer was diagnosed in 5 patients and presented at a mean age of 20.8 years (range 19 to 23 years). All patients were successfully treated with total thyroidectomy. Hepatoblastoma was diagnosed in 4 patients with a mean age of 18 months (range 9 to 24 months). Two patients developed late cardiac failure secondary to Adriamycin associated with treatment of infantile hepatoblastoma. Additionally, two patients were found to have brain tumors (1 craniopharyngioma at age 29 years and 1 glioblastoma at age 8 years). Both were successfully treated with surgical resection.

2.6. Survival

Six patients died from FAP related events during the study period. One patient died at age 34 years of an unknown cancer (death occurred elsewhere), but had high grade dysplasia in the rectum at the time of proctocolectomy. Two patients died from desmoid tumor spinal invasion (ages 22 and 32 years). An 8 year old died from chest wall invasion by a desmoid. A 21 year old died from cardiac failure secondary to Adriamycin they received as an infant for treatment of hepatoblastoma. And finally, an 18 year old who presented with advanced rectal cancer died at age 22 due to progression of metastatic disease.

3. Discussion

Herein, we describe a large, single institution's experience with FAP. While this study is limited by our institutional biases, we have reached several conclusions regarding screening and managing children with FAP. The first is that the age of presentation of colonic polyposis varies widely. Our youngest patient presented at age 8 months of age with blood per rectum due to high polyp burden. Her family phenotype was for early onset and rectal bleeding. The mean age of colon polyp diagnosis was 13 years; yet importantly we found that a significant number of patients had polyps prior to age 10 years and even age 7 years. We therefore routinely begin screening colonoscopy prior to the recommended 10 years of age, ideally around 7 years of age. If patients younger than 7 years present with symptoms such as rectal bleeding or if their family phenotype is early onset, we begin screening at any age before 7 years. We propose a screening and evaluation strategy (Fig. 1) for the clinical evaluation of patients with FAP based on our experience.

The second observation is that the polyp burden can vary significantly. Our endoscopists have found that these polyps are amenable to endoscopic therapy if the polyp burden is limited ($\leq$30 polyps). Just over 80% of our patients had pancolonic polyps, thus the best screening tool was colonoscopy instead of sigmoidoscopy. As we use anesthesia support for all of our elective endoscopic procedures, it seemed prudent to perform a full colonoscopy instead of sigmoidoscopy to determine the extent and the degree of polyp burden and if there are a limited number of polyps (30 or fewer) to perform polypectomy. Those not amenable to endoscopic management (greater than 30 polyps) or those with high grade dysplasia or invasive carcinoma were offered colectomy.

The third observation is that the familial pattern of occurrence can aid in determining an individualized screening and treatment program. Genetic profiling has progressed significantly in recent years and can help guide screening and operative management [7]. We have observed that family phenotype is indicative of polyp onset. Thus, if a first degree family relative had early onset of polyps or symptoms, we proceed with screening colonoscopy at the age of the youngest family member's polyps or symptoms. If this screening study is negative, a repeat study would be performed every 2 years; however, polyps have been identified in all our patients with early familial phenotype.

We advocate complete removal of the colon and rectum in pediatric cases of FAP as these virtually always have involvement of the rectum. The optimal age which proctocolectomy should be performed remains controversial. We encourage close screening and surveillance of patients with FAP throughout childhood as outlined above. All patients with high grade dysplasia or invasive adenocarcinoma on colonoscopy should proceed with proctocolectomy. We also recommend surgery when the polyp burden is >30 or when symptoms are present (pain, bleeding, etc). Social and developmental factors are also considered. With 5 cases of invasive cancer and 5 cases of high grade dysplasia $\leq$20 years of age, we advocate colectomy in the early teen years to prevent progression to these conditions. However, in patients with desmoid tumors, we prefer to delay colectomy until polyp burden exceeds endoscopic management.

Our preferred surgical approach for patients with FAP is laparoscopic total proctocolectomy with ileal pouch anal anastomosis (IPAA) with a mucosectomy and hand sewn anal anastomosis. We have observed good patient acceptance of this procedure, excellent functional results, and few postoperative complications [9]. We have seen no occurrence or recurrence of colorectal cancer in patients following total proctocolectomy with ileal pouch anal anastomosis. One patient required pouch excision due to early post-operative complications, however all other patients who underwent IPAA had a functional pouch at last follow-up. Frequency of bowel movements in patients after IPAA was highly variable, ranging from 1 to 6 bowel movements per day. Overall continence was excellent following IPAA. Occasional daytime leakage was experienced in 16% and occasional nighttime leakage in 10%, however no significant or complete incontinence was reported [9]. After IPAA patients should be followed with annual pouchoscopy for surveillance of anastomostic polyp recurrence.

In the modern era, most FAP patients are not developing colorectal cancer due to the widespread practice of early colectomy. Therefore, secondary causes of morbidity, such as duodenal adenocarcinoma are being encountered in the post-colectomy population [5]. More than half of our patients (59%) developed upper gastrointestinal (UGI) polyposis, with mean onset at age 17 years. None have progressed to invasive cancer to date. No age has been defined when to begin surveillance of the upper digestive tract in FAP patients. Our practice is to begin gastroduodenal surveillance via endoscopy at age 10 to 12 years, with repeat examination every 3 to 5 years. Alternative suggestions have been to begin upper endoscopy at initial evaluation, concomitant with colonoscopy [3,4]. We proceed with side viewing endoscopy for evaluation of the ampulla beginning at age 15 years.

Children with FAP may also develop benign extraintestinal manifestations, such as epidermal cysts, lipomas, osteomas and extranumerary teeth. These are not typically of significant medical concern, but may serve as diagnostic markers. Osteomas frequently

Table 4
Extraintestinal manifestations.

Extraintestinal manifestation	n (%)
CHRPE	18 (11.3)
Osteoma	11 (6.7)
Epidermal Cyst	9 (5.5)
Extranumerary Teeth	6 (3.7)
Papillary Thyroid Cancer	5 (3.1)
Hepatoblastoma	4 (2.5)

CHRPE = congenital hypertrophy of the retinal pigment epithelium.

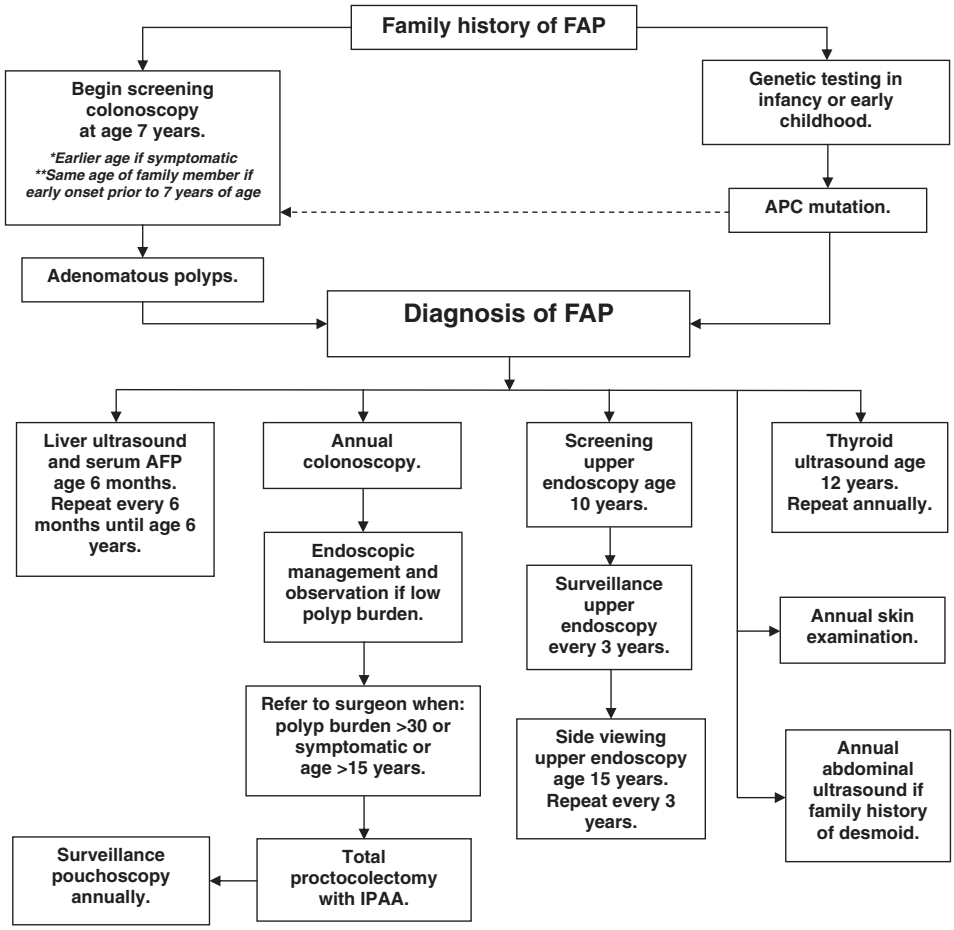

Fig. 1. Proposed familial adenomatous polyposis screening guidelines.

involve the jaw. Dentists should consider referral of patients with extranumerary teeth or jaw osteomas for FAP evaluation. Epidermal cysts and lipomas are common in the general population however their presence in children with a family history of FAP should prompt further investigation for other features of FAP [10]. Children from families with known FAP should undergo annual skin exam. Of note, superficial desmoid tumors may present similarly. Desmoids should be considered for any firm, fixed and/or rapidly growing skin or subcutaneous lesion.

Desmoids were identified in 18 (11%) of our patients. While these are not malignant tumors, they are locally aggressive. In fact, three of our patients died from complications of desmoid growth near vital structures. These masses are difficult to manage surgically as they tend to recur, and also medically since they do not respond well to chemotherapy. Previous report from our institution indicates that most desmoids are sporadic but 16% were associated with FAP. Those associated with FAP were more likely to be intra-abdominal [11]. Desmoids occurred at a variety of ages in our patients (range 2 to 31 years). We recommend screening for desmoids after abdominal surgery with annual abdominal ultrasound or after age 12 years in those with a family history of desmoids. Females tend to form desmoids more often than males with FAP, and early colectomy in girls before 18 years of age has been reported to double the likelihood of desmoid formation [12]. CHRPE is a benign finding encountered on funduscopic evaluation of 43%–58% of FAP patients [10,13]. There are no clinical sequelae of this condition but its presence should prompt further evaluation for FAP. However, CHRPE also exists in 5% the general population without FAP [13]. Routine funduscopic evaluation has not been part of our evaluation of pediatric FAP patients (hence our lower than expected incidence of CHRPE at 11%) due to its limited clinical relevance.

Papillary thyroid cancer was diagnosed in 3.1% of our patients. This is similar to previous report from adult data where 2.6% of FAP patients had papillary thyroid cancer [14]. FAP patients are also more likely (38%) to develop benign thyroid nodules [14]. Previous reports suggest thyroid screening with neck ultrasound beginning at age 16 years, however their youngest patient with PTC was 35 years old. Our youngest FAP patient with PTC was 19 years old, therefore we prefer earlier ultrasound thyroid screening beginning at age 12 years. Papillary thyroid cancer is sporadic in 90%–95% of cases, however, it may occasionally be due to genetic syndromes other than FAP. PTC has been associated with Cowden Syndrome (hamartomas, PTC, and breast masses) and familial clear cell renal cell cancer. Thorough family history should be obtained with genetic testing to confirm familial cases of PTC [15].

Hepatoblastoma was found in 4 of our young patients (ages 9 to 24 months); there were no infant fatalities amongst our patients. However, despite aggressive modern medical and surgical management, approximately 25% of patients with childhood hepatoblastoma will be fatal [16]. We therefore recommend aggressive liver screening of infants with known or suspected FAP. Liver ultrasound and serum AFP should be done by 6 months of age and be repeated every 6 months until age 6 years. Furthermore, children with hepatoblastoma should undergo genetic testing to look for an APC mutation [16].

We present one of the largest and most comprehensive reviews of pediatric familial adenomatous polyposis in the literature to date. While inherent institutional, referral, and patient selection biases

exist in this cohort, we recommend consideration of this screening algorithm to pediatric and surgical professionals treating pediatric patients with FAP. We will continue to investigate the relationship of genotype with phenotype in an attempt to further refine these guidelines.

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