Evaluation of Guidelines for Management of Familial Adenomatous Polyposis in a Multicenter Pediatric Cohort

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ABSTRACT

Objective: To retrospectively assess, in a pediatric multicenter cohort, guidelines for the management of familial adenomatous polyposis (FAP).

Methods: Ten centers from the French-speaking Pediatric Gastroenterology Hepatology and Nutrition Group provided follow-up data on patients up to 18 years of age. Clinical records, genetic test results, endoscopy with histopathology examination, and therapeutic modalities were reviewed.

Results: A total of 70 children from 47 families were included. When initial consultation resulted from a surveillance program because of an affected family member, 12 of 59 children were already symptomatic. Among 11 patients whose initial consultation was based only on symptoms, families were unaware at the time of a familial FAP history for 7 children, whereas only 4 cases were sporadic. A panel of 27 different pathogenic adenomatous polyposis coli (*APC*) germ-line mutations and large genomic deletions were identified in 43 families. Extracolonic manifestations were found in half of the patients. As part of the standard practice for initial screening, the entire cohort underwent colonoscopy, which revealed adenoma above an intact rectosigmoid in 8 cases. Prophylactic colectomy was performed in 42 cases; high-grade dysplastic adenoma and 1 invasive carcinoma were detected in 6 children. For timing of surgery, indications were in accordance with recent international guidelines.

Conclusions: Defining optimal screening and therapeutic modalities in pediatric FAP cohorts is a challenge. Specific advice for genetic screening, endoscopy surveillance, and type of surgery based on recent guidelines is recommended.

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Familial adenomatous polyposis (FAP) is a highly penetrating autosomal-dominant colorectal cancer (CRC) syndrome with significant morbidity and mortality. This rare disease, which occurs in 1 of 10,000 births (1), is characterized by early onset of numerous adenomatous colorectal polyps and several extracolonic manifestations. Left untreated, there is nearly 100% progression to CRC by age 35 to 40 years. Increased risk of malignancy at other sites, including the brain, thyroid, and liver, has been reported. This inherited syndrome is caused by a germ-line mutation in the *APC* gene, located on chromosome 5q21 (2). Around 15% to 30% of cases are de novo, with no clinical or genetic evidence of FAP in the parents (3). More than 800 mutations have been described, with some genotype–phenotype correlations; however, heterogeneity exists in the clinical course, even among family members with the same mutation.

In pediatrics, only small series or case reports (4–12) have been reported. The aim of the present study was to collect a large pediatric multicenter cohort with follow-up to 18 years of age. Clinical presentation, genetic analysis, endoscopy, and histological reports and outcome were assessed. International recommendations (13,14) are discussed here because challenges lie in defining both optimal surveillance and therapeutic modalities.

PATIENTS AND METHODS

Study Centers and Inclusion Criteria

Members of the French-speaking Pediatric Gastroenterology Hepatology and Nutrition Group were asked to include all of the patients 18 years or younger regularly studied for FAP, with the presence of an *APC* gene mutation (family history or de novo mutation) or with adenomatous colorectal polyposis and an unidentified gene mutation. A letter of information was sent by the referring physician to the selected patient's parents, who were free to reject participation by sending back the document with their signature. The National Committee of Liberty and Information approved the protocol for anonymous data collection and analysis (Ref.MCB/AB/no.107.00, 03/03/2004).

Questionnaire

The study centers provided the following items on a standardized questionnaire: age, sex, description of family history, age

and symptoms at initial consultation, and associated extracolonic manifestations. Initial and subsequent colonoscopies, esophagogastroduodenoscopies (EGD) with macroscopic findings, and histopathology data were recorded. Polyps were classified according to their number (none, few, numerous [≥50 polyps], innumerable or ''carpeted''), size (<0.5 cm, 0.5–1 cm, >1 cm), and location (rectosigmoid, left colon, midcolon, right colon, ileum, gastric, duodenum, and unexplored region). Histopathology results were not centrally reviewed; pathologists at their own institutions graded adenoma dysplasia as low, mild to moderate, high, or severe and invasive carcinoma. Histopathology reports were centrally reviewed if high-grade dysplasia or invasive carcinoma was reported. Treatment data included, when necessary, age and type of colectomy (subtotal colectomy with ileorectal anastomosis [IRA], total proctocolectomy or ileal pouch anal anastomosis [IPAA]), postsurgical complications, follow-up (medication, bowel movements), and, if the patient died, age and cause of death. All of the patients or legal representatives signed informed consent for a genetic examination after an interview with an authorized geneticist. Mutation analysis was performed at the same center (SO). After genomic DNA extraction from peripheral blood samples, the entire coding sequence of the *APC* gene was screened by sequencing according to previous reports (15). Search for large genomic rearrangements was performed using the quantitative multiplex polymerase chain reaction of short fluorescent fragments technique as developed by Demange et al (16).

Statistical Analysis

Statistical analysis was carried out using SAS version 9.12 software (SAS Institute, Cary, NC). Qualitative variables were described as numbers and percentages and quantitative variables as medians with their quartiles (Q1–Q3). Differences were tested by Fisher exact test for categorical variables and by Wilcoxon test for quantitative variables. Time to colectomy was assessed by the Kaplan-Meier curve.

RESULTS

Between March 2005 and December 2007, a total of 70 patients from 10 centers (9 in France, 1 in Belgium) were included in the database. No families refused to participate in the study. There were no duplicates. The oldest patient was born in 1970 and the youngest in 1995. Table 1 provides characteristics of the cohort issued from 47 families according to clinical or genetic evidence of FAP in parents. All of the patients were alive at the time of chart analysis.

Clinical Presentation

Among the 66 patients with familial FAP (Table 1), 59 had an initial consultation within the framework of a surveillance program for families of an affected member and 12 of these were already symptomatic. The other 7 children had developed symptoms before FAP diagnosis; families were unaware at that time of an FAP history. Median age at diagnosis was younger in the symptomatic group (8.8 years [6.5–10.1]) than in the ''surveillance asymptomatic'' group (10.3 years [7.6–12.3]), although this difference was not found to be statistically significant. A small cohort of 4 symptomatic children represented de novo mutation patients seen at a median age of 11.3 years [8.9–13.4].

In the overall cohort, 23 patients (33%) were symptomatic at diagnosis, mainly with rectal bleeding (73%), abdominal pain (36%), anemia (14%), and diarrhea (14%), whereas 1 presented with costal osteoma.

TABLE 1. Familial adenomatous polyposis population characteristics

Variables	No.	%
Patients, sex (n = 70)		
Male	34	48.5
Female	36	51.4
Family history (n = 47)		
Positive	43	9.5
Negative	4	8.5
Clinical presentation		
Familial FAP	66	94
Surveillance program, asymptomatic	47	71
Surveillance program, symptomatic	12	18
Symptomatic	7	10
De novo FAP	4	6
Symptomatic	4	100

FAP = familial adenomatous polyposis.

Colonoscopy and Histology Findings

Median age at initial colonoscopy was similar in familial FAP and de novo cases, respectively 9.7 (7.6–12.4) and 11.7 (9.1–13.9) years. A total of 245 procedures were performed before the patients were 18 years of age, with a median number per patient of 2 (range 1–11), and histopathology reports were available for 85% of them. The median duration between initial colonoscopy and the final procedure was 7 (2–10) years (with a total of 494 follow-up years). Colorectal adenomas were identified in initial colonoscopy in 80% of the cohort, with this percentage reaching 93% in subsequent colonoscopy. In all of the patients presenting with rectal bleeding, polyps were found at initial colonoscopy; thus in our cohort, rectal bleeding predicted the likelihood of dysplasia. It is noteworthy that in 8 children, colonic polyps were found above an intact rectosigmoid, with 2 children presenting rectal bleeding at 8.5 and 9.5 years of age. Polyp sizes were under 0.5 cm in all of the patients but 5; 4 had a polyp size between 0.5 and 1 cm (2 high-grade dysplastic polyps) and 1 patient had a polyp >1 cm (moderate-grade dysplasia). Innumerable polyps were identified in 25 patients. Histopathology results on preoperative endoscopy and surgical specimens from the 42 patients who underwent prophylactic colectomy are summarized in Table 2. Exploration above the ileocecal valve was carried out in 72% of colonoscopies, thus possibly underestimating the extent of ileal polyps. One ileal low-grade dysplastic polyp was identified before any surgical procedure and remained stable during the 7-year follow-up. Regular endoscopic surveillance after both types of surgery found low-grade dysplastic polyps in the ilea of 2 patients who underwent IPAA (remaining stable after 2- and 3-year follow-up, respectively) and in the recta of 2 patients with IRA.

Extracolonic Manifestations

A total of 60 extracolonic manifestations were identified in half of the cohort (Table 3). Desmoid tumors developed in 5 patients at as early as 1.1 years of age. Follow-up remained uneventful for all but 1 patient, who developed a mesenteric tumor that led to compression symptoms and required surgery and conversion to IPAA 3 years after prophylactic IRA colectomy was performed in the late 1980 s. Osteomas and epidermoid cysts were also reported; nevertheless, they may not have been thoroughly noted on the chart

TABLE 2. Colon histopathology data on the 42 patients with PAF who underwent prophylactic colectomy

Pathology	No.	%
Preoperative endoscopy (n = 42)		
Dysplasia*	41	100
Invasive carcinoma	0	0
High-grade	3	7
Low to mild to moderate grade	38	93
No dysplasia	0	0
Surgical specimen (n = 36)		
Dysplasia	37	100
Invasive carcinoma	1	2.8
High-grade	4	11
Low to mild to moderate grade	31	86
No dysplasia	0	0
Overall (n = 42)		
Dysplasia	42	100
Invasive carcinoma	1	2.4
High-grade	5	12
Low to mild to moderate grade	36	85.6

* Data were not available for 1 patient.

by the gastroenterologist caring for patients with FAP because of their low morbidity.

Congenital hypertrophy of the retinal pigment epithelium (CHRPE), a highly specific phenotypic manifestation of the disease and a predictor of the presence of FAP, was identified in 14 of the 31 documented families.

EGD was performed as part of the evaluation in 54 patients, with a total of 155 procedures. Fundic (n = 3) and/or antral (n = 4) gastric adenoma was present in 11%. Duodenal adenomas were found in 23 patients (43%), with the youngest patient being 6.9 years old; all of the polyps were stage I Spigelman (17) with remarkable stability of dysplasia during the follow-up period (median duration 7 years [2–10]). One hepatoblastoma was reported in a 1-year-old girl. One child had acute lymphoblastic lymphoma at 3 years of age with complete remission.

Surgery and Follow-Up

Forty-two patients (60%; 18 boys and 24 girls) underwent prophylactic colectomy. Median ages at surgery were, respectively, 13.5 (10.9–14.7) and 12 years (9.4–14). Figure 1 shows the risk of colectomy according to age with a median of 14.9 years (95% confidence interval 13.9–15.7); no significant difference was observed according to date of birth.

For 25 patients, the decision for surgery relied on innumerable polyps, all with evidence of low- or moderate-grade dysplastic foci except for 1 with high-grade dysplasia (at 11.6 years); for 11 cases, the decision was based on numerous polyps with a sharp increase in polyp development in association with rectal bleeding in 6 patients, or else the ''hot-spot'' 1309 mutation. Finally, indication relied on high-grade dysplasia on preoperative endoscopy in 2 children (at 13.8 and 15.5 years) and on severity of disease expression in 4 families (hepatoblastoma [1], glioblastoma in a sibling [1], father's recent death [2]).

Surgery was performed on 39 children with a familial history of FAP (58%) and on all de novo mutation patients. The surgical procedure consisted of IRA for 14% and IPAA for 86%. The percentage of patients experiencing complications was similar whatever the type of surgery, with discrepancies in their manifestations (Table 4). Locoregional infections, septicemia, postsurgical abdominal wall desmoid tumors, and soiling after a 6-month delay occurred only following the IPAA procedure. After IRA, the only complication was postoperative small bowel obstruction, observed in 3 patients. Long-term medical maintenance therapy to reduce the average number of bowel movements was required in 39% of patients with IPAA. None of the children received postoperative chemoprevention with NSAIDs or selective cyclooxygenase-2 inhibitors.

Overall, 6 patients (8.5%), all with a family history of FAP, presented high-grade dysplasia, with 1 invasive carcinoma at 8.8 years. Diagnosis was made based on endoscopic biopsies in 2 children with polyp size >0.5 cm and in 1 child with innumerable polyps. For the remaining 3, diagnosis was based on surgical specimens: The indication for prophylactic colectomy was based on rectal bleeding for 2 patients and innumerable polyps for 1 (Table 5).

None of the patients who underwent IRA developed high-grade adenoma in the rectum during follow-up (median duration 9 years [6–10]). No pouch adenoma was found during regular follow-up after IPAA. Ileal low-grade dysplastic adenoma occurred in 2 patients.

Mutation Analysis

Pathogenic germ-line *APC* alterations and large genomic deletions were identified in 43 of the 47 families (84%), with a detection rate, which attained 100% in patients with de novo mutation. Most alterations (37 of 42) were predicted to lead to truncated *APC* proteins, including 20 frameshift mutations caused by small deletions/insertions, 16 nonsense mutations, and 1 mutation involving a consensus-splicing site. A total of 27 different mutations and 5 genomic deletions were identified (Table 3). Attenuated FAP (AAPC) arising from *APC* gene mutations in the extreme proximal 5′ to codon 168 was present in 1 family. Mutations between codons 1250 and 1464, usually described for the classical severe phenotype, involved 16 families with 24 children. Mutational ''hot-spots,'' mainly at codons 1309 and 1061, were present, respectively, in 10 families (15 patients) and 1 family (2 patients). Mutations at other sites usually involved patients with classical phenotypes; they characterized 21 families and 25 children. Large genomic deletions were found in 5 families (7 children); up until now, only 4 families (11 children) have been found to be phenotype-positive, genotype-negative. Incomplete gene analysis in 1 family resulted from insufficient biological material.

Genotype–Phenotype Correlations

Genotype–phenotype correlations described in the literature mainly involved epidemiological data with long-term follow-up of patients through adulthood. In our pediatric cohort, we may have missed information on items that developed with increasing age.

In families (Table 6) with codon mutations usually associated with a classical severe phenotype, 81% underwent colectomy before 18 years of age. For specific hot-spot mutations at codon 1309, although 60% were clinically symptomatic, with 82% of them having innumerable colorectal polyps at the time of prophylactic colectomy, none presented with high-grade polyp dysplasia. Two patients with the hot-spot mutation at codon 1061, clinically asymptomatic but with innumerable polyps for 1 of them, refused surgical treatment at the time of the study at 16 and 17 years of age, but were followed up by a psychologist. In the remaining patients with a mutation associated with a classical severe phenotype, 33% were clinically symptomatic, 66% underwent colectomy, and a high-grade dysplastic polyp was reported in a 16.2-year-old patient.

TABLE 3. Clinical and genetic characteristics of the 49 PAF families

FAP families	No. cases	Initial symptoms	Codon mutation	Transmission	Extracolonic manifestations	Surgery/high grade/carcinoma
1	3	0	1362	F	D (2), A (2), CHRPE, Ds (2), EC	IPAA (2)
2	2	0	936	M	D (1), A (1), CHRPE	IPAA (2)
3	2	0	1061	M	D (2), CHRPE	0
4	2	0	1065	F	D, CHRPE	IPAA (2)
5	1	0	1538	M	D, EC,	IPAA, HG
6	1	0	696	F	D, CHRPE	IPAA
7	1	1	1309	—	D, F, CHRPE	IPAA
8	1	1	1309	F		IPAA
9	1	1	1062	F		IPAA, HG
10	1	1	1406	—	D, A	IPAA
11	1	0	del complete	F	D	0
12	1	1	235	M	D, F	0
13	2	0	del complete	M		IPAA
14	1	0	984	F		IPAA, HG
15	1	1	1420	F	EC	0
16	2	1	1556	M	D	IPAA (1)
17	2	1	NI	M		IRA (2), IC (1)
18	1	0	936	M	D, F	0
19	1	1	1564	—	Ds	IRA
20	1	0	del complete	M		IPAA
21	1	0	499	M		0
22	2	0	158	M		0
23	2	0	215	M	D	IPAA (2), HG (1)
24	1	0	564	F	CHRPE	IPAA
25	1	0	136	M		0
26	5	0	NI	M		IPAA (1)
27	3	1	1309	F	CHRPE, EC	IPAA (3)
28	1	1	1370	M		0
29	1	1	1370	F		IRA
30	1	0	1309	F		IPAA
31	2	1	943	F		0
32	1	1	1309	F		IPAA
33	1	0	876	F	CHRPE	0
34	1	0	1567	M	D, CHRPE, Ds, EC	0
35	1	0	216	F		IRA
36	1	1	1309	—		IPAA
37	1	1	213	M	H	IPAA
38	1	0	NI	F		0
39	2	1	1309	M	CHRPE, Ds	IRA (1), IPAA(1)
40	2	1	del complete	F	D (2), CHRPE	IPAA (1)
41	1	1	1396	F		0
42	1	1	1309	F		IPAA
43	3	0	NI	M	CHRPE, EC	IPAA (2)
44	1	1	1309	F	D	IPAA
45	3	1	1309	M	D (3)	IPAA (3)
46	1	0	805	F	D	IPAA, HG
47	1	0	del 8–15	M		0

Initial symptoms: presence: 1, absence: 0. Codon mutation: NI = nonidentified. Genetic transmission: F = father; M = mother. Extracolonic manifestations: A = antral adenoma; CHRPE = congenital hypertrophy of the retinal pigment epithelium; D = duodenal adenoma; Ds = desmoid tumor; EC = epidermal cysts; F = fundic adenoma; H = hepatoblastoma. Adenoma dysplasia: HG = high-grade dysplasia; IC = invasive carcinoma. Surgery: IPAA = ileal-pouch anal anastomosis; IRA = ileorectal anastomosis.

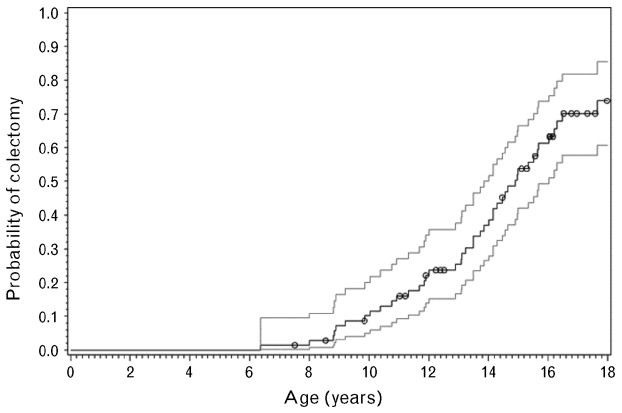

FIGURE 1. Time to colectomy (estimated by the Kaplan-Meier curve).

Codon mutations located at other sites were usually associated with classical phenotypes; 56% underwent colectomy; and, surprisingly, 4 high-grade adenomas were identified at 11.6, 12, 13.8, and 16 years of age in asymptomatic children, 2 of whom presented with innumerable polyps and 2 who had polyps larger than 0.5 cm. Codon mutations usually associated with AAPC were found in only 1 family. In patients with large genomic deletions or from genotype-negative families, rates of colectomy were, respectively, 43% and 33%. Thus, our data confirm important phenotypic discrepancies in the severity of the disease within each of these subgroups, even among patients with identical mutations.

Extracolonic manifestations were found in 49% of the patients. Desmoid tumors were associated with a codon mutation located at the 3′ end of the *APC* gene in 75%, as previously reported. CHRPE was identified in families with mutations between codons 311 and 1444, as described in the literature, but 5 families screened negative even though they had a mutation within this range. The patient who developed a hepatoblastoma had a mutation in the proximal half of the *APC* gene.

DISCUSSION

We describe here the largest series of children ever diagnosed as having FAP. Previous reports mainly involved small cohorts, and most of them were published before the era of genotyping (4–8) or were case reports (9–12). The role of molecular testing for at-risk members in childhood in case of mutations that predispose to early onset of FAP has been emphasized (18–22), leading to recently published guidelines for the clinical management of FAP.

TABLE 4. Short- and long-term complications after prophylactic colectomy

Procedure	IRA	IPAA
No. colectomies (%)	6 (14)	37 (86)
No. patients with complications (%)	3 (50)	16 (44)
Short-term complications (%)	3 (50)	17 (47)
Pelvic abscess	0	5
Anastomotic separation	0	3
Septicemia	0	2
Postoperative bowel obstruction	3	4
Anal stenosis	0	1
Pelvic hematoma	0	1
Pancreatitis postlaparoscopic healing	0	1
Long-term complications (%)	0	3 (8)
Daytime/nighttime soiling	0	1/1
Intrabadominal desmoid tumor	0	1
Medicine prescription (%)	0	14 (39)

IPAA = ileal pouch-anal anastomosis; IRA = ileorectal anastomosis.

TABLE 5. Percentage of colectomy and occurrence of high-grade adenoma dysplasia/invasive carcinoma according with the genotype

	Patients	Colectomy (%)	HG/IC
Total	70	42 (60)	6
Familial history	66	38 (58)	6
De novo mutation cases	4	4 (100)	0
Classical severe genotype	24	21 (81)	1
Hot-spot mutation 1309	15	15 (100)	0
Classical genotype	25	14 (56)	4
Attenuated FAP	3	1 (33)	1
Large genomic deletion	7	3 (43)	0
Negative genotype	11	3 (33)	0

FAP = familial adenomatous polyposis; HG = high-grade adenoma dysplasia; IC = invasive carcinoma.

Several studies recently reviewed by Nieuwenhuis et al (20) showed that the severity of colonic polyposis partly depends on the mutation site. Thus, mutations between codons 1250 and 1464 with the 2 identified hot-spot mutations at codons 1309 and 1061 are associated with a classical severe phenotype (thousands of polyps). In those patients, bowel symptoms and neoplastic disease tended to develop more than 10 years earlier and patients had significantly more colorectal polyps at the time of colectomy (21). Conversely, mutations before codon 157, after codon 1595 and in the alternatively spliced region of exon 9, were usually associated with an attenuated form of FAP (AFAP) (<100 colorectal polyps) and CRC at a more advanced age (23); in the remainder of the gene, a classical phenotype (100–1000 polyps) usually has been described. It should be borne in mind, however, that the site of mutation will not necessarily predict a certain gene product with a subsequent phenotype. Although general correlations can be established, inconsistencies and contradictions have been extensively reported (13,24), thus limiting the interpretation of genotype–phenotype relations.

In our cohort, half of the 15 children with a hot-spot codon mutation located at 1309 had undergone prophylactic colectomy before age 11 years, earlier than recommended in the literature (3), thus, perhaps, preventing malignant changes. Four of the 6 patients with high-grade dysplastic adenoma presented a mutation usually associated with a classic phenotype (age range 12–16 years) and colonoscopy overlooked severe dysplasia in 3 cases, pointing first to the difficulty in endoscopically diagnosing severe lesions when numerous or innumerable polyps are present, and second, to the lack of an association between polyp size and the degree of dysplasia, as previously reported (25,26).

Colectomy remains the optimal prophylactic treatment; however, the timing of surgery has not yet been standardized because patients and families differ in the severity of disease expression and the social context (13). It is tempting to delay surgery until children mature physically and finish school; nonetheless, there is concern about CRC in teenagers when surgery is deferred. Thus far, the literature has provided little information on the age distribution at diagnosis of CRC in FAP patients younger than 20 years because most cases are diagnosed at a premalignant stage. Before the era of genotyping, Peck et al (5) reviewed the literature and identified 10 pediatric CRC. Later, Hyer et al (18) found a 3% occurrence of

TABLE 6. Patients' characteristics with high-grade adenoma dysplasia/invasive carcinoma

Symptoms	Codon mutation	Preoperative endoscopy	Colectomy, y	Specimen
No	215	Innumerable polyps HG	11.5	HG
No	805	Polyps >0.5 cm HG	13.8	HG
No	1538	Polyps >0.5 cm HG	16	—
No	984	Innumerable polyps	12	HG
Rectal bleeding	NI	Numerous polyps	8.8	IC
Rectal bleeding	1406	Innumerable polyps	16.2	HG

HG = high-grade adenoma dysplasia; IC = invasive carcinoma; codon mutation: NI = nonidentified; —.

severe dysplasia in a cohort of 13 patients 11 to 16 years of age, all of whom presented significant gastrointestinal symptoms, in contrast to our study results (2 rectal bleedings of 6). Surprisingly, in a small monocentric cohort of 11 teenagers (22) who underwent prophylactic colectomy at a mean age of 13 ± 3.2 years, a high rate of severe dysplasia (27%) was reported. Recently, Church et al (8) surveyed 16 polyposis registries to assess the risk of CRC in teenagers; the estimated calculated incidence was 1 case per 471 patients with FAP younger than 20 years of age. Fourteen cases were identified (the youngest was 9 years old), all of them presenting with severe phenotypic polyposis (defined as more than 1000 colonic polyps), whereas 36% were clinically symptomatic. Vasen et al (13) reported data from several European registries, which included more than 1000 patients younger than 20 years; they found a low proportion of patients with FAP with CRC (0–10 years: 0%, 11–15 years: 0.2%, 16–20 years: 1.3%). Prospective studies comparing early surgical intervention with standard care management in the younger FAP population would help to clarify this issue, but are ethically impractical. Unfortunately, none of these studies provided data on gene mutation analysis.

In recent international guidelines (13), prophylactic colectomy is recommended if there are ''large numbers of adenomas larger than 5 mm including adenoma showing a high degree of dysplasia.'' We agree with the authors who stated that the majority of patients with classical FAP should undergo surgery between 15 and 25 years of age. Conversely, Barnard (14), in his recent article on pediatric FAP, suggests a more aggressive attitude: ''Once adenomas are identified, it is recommended that ileal pouch anal anastomosis or ileal anastomosis be performed''; however, that statement does not indicate the patient's genotypic data, nor is a specific bibliography provided.

The choice between the 2 types of surgical procedure (28) had been controversial until recent guidelines began to approach a consensus, (13), suggesting use of the outcome of genetic testing to guide the choice between IRA and IPAA (20–29). IPAA is now advisable in patients with a mutation located distal to codon 1444. Indeed, such patients are at risk of desmoid tumors, and conversion of IRA to IPAA may be difficult in cases of asymptomatic mesenteric desmoid tumors or in patients with a severe genotype because they have an increased risk of developing severe rectal polyposis that would require secondary protectomy if IRA were performed. In our cohort, 4 patients (2 with innumerable rectosigmoid polyps, 2 with desmoid tumors) should have undergone IPAA, but this was in the late 1980s and they were unable to benefit from genetic testing at that time. Recently, a meta-analysis on quality of life after those 2 surgical options (27) was in favor of IRA (bowel movement frequency, reoperation within 30 days); IPAA, which implies more extensive surgery, including pelvic dissection, has a higher morbidity rate with possible reduction in fertility (28), although the latter hypothesis is controversial.

Most patients with FAP develop extracolonic manifestations over time; at present, a higher proportion of deaths in adulthood may even be attributed to desmoid or duodenal tumors (30) rather than to CRC. Desmoid tumors (31), although benign, can lead to compression of vital organs. Adenomatous gastroduodenal polyps are common, with rates approaching 100% over time, and only a small fraction will develop invasive cancer in adulthood (3%–5%) (32). Scott et al (33) found duodenal adenomas in childhood at the same frequency as in our cohort; an association between a germ-line *APC* mutation and severity of upper gastrointestinal (GI) polyposis remains controversial (34) and only future large multicentric studies will provide confirmation. In accordance with international guidelines, upper GI polyposis surveillance should begin when colonic adenoma is identified (14) or between the ages of 25 and 30 years (13), with intervals between screening in stage I Spigelman of 5 years; indeed, prospective studies demonstrated the slow progression of duodenal polyp size, number, and histology (35). In our study, most patients underwent upper GI, with a median of 3 procedures, pointing to possible overscreening by pediatric teams. An endoscopic retrograde cholangiopancreatographic side-viewing endoscopy is recommended to enable detailed inspection of the papilla for ampullary carcinoma detection; however, in early Spigelman stages typical of the pediatric population, the use of a forward-viewing endoscope is considered appropriate (13). Optimal surveillance protocols for genetic counseling, types of investigation, and surveillance intervals in patients with FAP and AFAP have recently been proposed (13,14). Predictive testing for the mutation should be offered to first-degree relatives in cases of typical FAP; however, the right age for screening of children at risk of FAP remains subject to careful consideration (36,37). In fact, early knowledge of the child's disease status may have detrimental effects on the family (37). Thus, some authors advise delaying the process until the child is old enough to take part in the decision (18); on the contrary, the prognosis has improved substantially for families under regular surveillance, because CRC is rare and occurs mainly in those with de novo mutations.

Guidelines for colonoscopic surveillance (13,14) recommended that family members who carry the mutation should undergo periodic examination of the rectosigmoid starting in the early teens. They also recommended starting earlier than 12 years of age in families in which severe dysplasia or carcinoma was found at a young age or in families with mutations associated with a severe phenotype (ie, 1309, 1061). In those guidelines, it was recommended that flexible sigmoidoscopy be performed, at least initially; once adenomas have been identified by sigmoidoscopy, there is an indication for full colonoscopy. Those recommendations were based on a study by Bussey et al (38) in the late 1970s, which demonstrated that in adults, the rectum was affected in all cases of colonic adenoma, thus recommending colonoscopy only after the appearance of rectosigmoid polyps. In our study, all of the centers immediately investigated the entire colorectum, in contrast to previous conclusions in adult studies; among the 8 patients with initial intact rectosigmoid, 3 would have had an initial colonoscopy in any case because of a rectal or severe genotype; for the 5 remaining patients, therapeutic intervention would not have been

different in cases of delayed colonoscopy until detection of rectosigmoid polyps. This is the first retrospective study demonstrating that we can safely use international adult guidelines for pediatric cohorts. Performing colonoscopy under general anesthesia in children may provide less discomfort than rectosigmoidoscopy, and this should be determined case by case.

Additional recommendations included an interval of 2 years between normal rectosigmoidoscopy and, if adenoma is detected, yearly colonoscopy until colectomy is required. In AFAP, a different protocol is advised because no CRCs have been described in patients younger than age 30 years; periodic examination should begin at 18 to 20 years of age with a colonoscopy because only a few adenomas develop, mainly in the right part of the colon (39).

Our data suggest that endoscopic surveillance in children with FAP should be modified according to recently recommended international guidelines, although in terms of surgical timing, indications were in complete agreement with those guidelines. Taking into account molecular-phenotypic correlations and family history, it is appropriate to provide specifically tailored advice for genetic counseling, endoscopic surveillance, and choice between the 2 types of surgical procedures; moreover, first-line management by pediatric gastroenterology teams should be determined case by case. Ideally, such patients should be studied at centers specializing in rare digestive diseases. Such structures have accumulated a critical mass of data, enabling the best possible patient care. They participate in well-established national and international registries and in networking activities for clinical and basic research.

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