ORIGINAL ARTICLE

Natural history of colonic polyposis in young patients with familial adenomatous polyposis

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Background and Aims: Proctocolectomy prevents colorectal cancer in familial adenomatous polyposis (FAP). Colorectal polyp progression is one of the indications for surgery. No data exist regarding the natural history of colorectal polyposis in young patients with FAP. This study examined the rate of polyposis progression and factors associated with it.

Methods: Patients with FAP <30 years old who had undergone ≥2 colonoscopies since 2000 were identified. Rate of polyposis progression was calculated by review of polyp counts obtained from baseline and last colonoscopy, accounting for any polyps removed during the observation period. Endoscopic and non-endoscopic factors affecting the rate of polyposis progression were evaluated. Multivariate analysis was performed to identify factors associated with rate of polyposis progression.

Results: One hundred sixty-eight patients (52% female; median age, 13.5 years) were included. Median rate of polyposis progression was 25.4 polyps/year (interquartile range, 9.5-69.8). Highest median rate of polyposis progression (89 polyps/year) was associated with mutation in codon 1309. The rate of polyposis progression was independently associated with the location of mutation in the *adenomatous polyposis coli* gene, the number of polyps at the initial colonoscopy, and exposure to chemoprevention. Of the 39.9% of patients who underwent surgery, an increase in polyp number was the most common indication (53.7%).

Conclusions: The rate of polyposis progression in young patients with FAP varies with a median of about 25 new polyps per year. Progression is associated with distinct factors, which can be used in discussion with patients regarding the need for and timing of prophylactic colorectal surgery. (Gastrointest Endosc 2018;■:1-8.)

INTRODUCTION

Familial adenomatous polyposis (FAP) is caused by a deleterious germline mutation in the *adenomatous polyposis coli* (*APC*) tumor suppressor gene.[1] The leading cancer risk in FAP is colorectal cancer (CRC).[2] Prophylactic proctocolectomy effectively prevents CRC and results in a similar life expectancy to the general population up to 18 years after surgery.[3,4] The optimal time for surgery should be early enough to prevent CRC but at the same time minimize the impact of surgery on quality of life, financial, academic, psychosocial, and physical factors.[5-7]

Published guidelines recommend surgery if CRC or colorectal symptoms are present,[8] but the indications in

Abbreviations: APC, adenomatous polyposis coli; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; FAP, familial adenomatous polyposis; GPC-Loc, genotype-phenotype correlation based on the location; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.

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asymptomatic patients are less clear. Guidelines suggest surgery for a significant increase in polyp burden,[8] but "significant increase in polyp burden" is not well defined. This study aims to quantify the natural history of polyposis in young patients with FAP and to determine factors associated with polyp progression.

METHODS

The Cleveland Clinic Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia maintains an Institutional Review Board-approved database (Cologene). This database, which exists within the David G. Jagelman Inherited Colorectal Cancer Registry, contains demographic, genetic, and procedural information on patients diagnosed with hereditary CRCs. Data on patients who consent to enroll in the registry are entered by the hereditary colon cancer registrars (L.L. and M.O.). The Cologene database was queried to identify all patients with FAP who were less than 30 years of age at the time of diagnosis and who had their first colonoscopy after 2000. Patients who had undergone 2 or more colonoscopies were included. Patients enrolled in randomized control trials related to chemoprevention were excluded. Demographic and clinical factors were verified using patient electronic medical records (Epic, Verona, Wisc, USA). The Jagelman Registry is approved yearly by the Institutional Review Board of the Cleveland Clinic. All patients sign informed consent at enrollment, which allows use of anonymized data for research. No patient contact took place for the purposes of this study.

Definitions

Rate of polyposis progression was calculated using the following formula: rate of polyposis progression = (number of polyps documented at last colonoscopy + total number of polyps removed during surveillance − number of polyps documented at first colonoscopy)/(years elapsed between the first and last colonoscopies). The addition of "total number of polyps removed" in the equation allows for assessment of the natural history of polyposis while controlling for polypectomy.

For all patients, demographic factors including age at first colonoscopy, gender, and body mass index (BMI); and clinical factors including personal or family history of desmoids, genotype-phenotype correlations (see below), de novo nature of *APC* mutation, family history of CRC; and colonoscopic factors including number of polyps at initial colonoscopy, presence of advanced adenomas (defined as at least one of the following criteria: >9 mm in size; with high-grade dysplasia; tubulovillous or villous histology), location of polyp predominance (defined as >50% of polyps proximal to the transverse colon (right side of colon predominant), >50% of polyps from splenic flexure to sigmoid colon (left side of colon predominant), or equal number of polyps on both sides) were identified. Genotype-phenotype correlations were studied based on the location (GPC-Loc) of the mutated *APC* codon as previously described by Nieuwenhuis et al.[9] Exposure to chemopreventive medications was defined as exposure to sulindac, celecoxib, or other nonsteroidal anti-inflammatory drugs (NSAIDs) for more than 3 months.

Colonoscopy protocol

Almost all patients <17 years old were examined with the patient under a general anesthetic. Older patients were usually examined under moderate sedation in an outpatient endoscopy suite. Most of the examinations were performed by one of the 2 main colonoscopists (C.B. or J.C.), who counted polyps according to segment of the colon. All visible polyps were counted, and note was made of the number and size of polyps removed. All polyps estimated as 5 mm or larger in greatest diameter and otherwise suspicious polyps (bleeding, ulcerated, or irregular) were removed. Patients undergoing their first colonoscopy had 1 or 2 polyps removed to document the diagnosis of adenomatous polyposis.

Criteria for surgery included symptoms likely to be due to polyps (bleeding, diarrhea, significant cramping in the context of a polyp load consistent with the symptoms), adenomas with high-grade dysplasia, adenomas too large or awkward to remove, multiple adenomas >2 cm, or a sudden increase in the number of adenomas. Factors encouraging surgical delay included a high risk of desmoid disease (family history of desmoids, *APC* mutation 3′ of codon 1400, extracolonic manifestations of Gardner syndrome) and the presence of social, academic, financial, or psychologic factors in the patient or family that made deferral of semi-elective surgery desirable.

Statistical analysis

Baseline patient characteristics were described. Rate of polyposis progression between patients who were and were not exposed to chemopreventative medications was computed. Next, patients exposed to chemopreventative medications were excluded (because exposure to chemoprevention can confound our aim to describe the natural history of polyp progression), and the rate of polyposis progression was calculated based on demographic, clinical, genetic, and colonoscopic factors. Significance of differences in the rate of polyposis progression was assessed using the Kruskal-Wallis test when more than 2 categories were present and the Mann-Whitney U test when only 2 categories were present. Continuous variables were reported as medians with interquartile range (IQR; 25th and 75th percentiles). Categorical variables were reported as frequencies with percentages.

After sorting patients by ascending order of mutated *APC* codon location, patients were clustered into groups of at least 5 patients. The median rate of polyposis progression for each of these groups was calculated and plotted as a line graph. This part of the analysis also excluded patients