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Original article

The epidemiological and clinical features of familial adenomatous polyposis in Ribeirão Preto☆

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ABSTRACT

Purpose: to study 75 familial adenomatous polyposis (FAP) patients treated in a single institution in Ribeirão Preto/SP, from January 1981 to December 2011.

Methods: this is a retrospective study and the following data were collected: gender, age, main symptoms, familial history, coexisting malignancies, surgical treatment, surgical morbidity and mortality, factors related to life quality.

Results: median age was 29 years. Male-to-female ratio was 1.2:1. Bleeding was the most common symptom (62.6%). Colorectal cancer incidence was 25.5% (n = 19). Extracolonic neoplasia incidence was 8%. Colectomy with ileorectal anastomosis (IRA) was performed in 72% of the patients. Eighteen patients (24%) were submitted to proctocolectomy with "J-pouch" ileoanal anastomosis. In three patients (4%) proctocolectomy with terminal ileostomy was performed. Early and late complication rate were similar (22.7% × 24%). Ileal pouch surgery exhibited tendency to a higher morbidity and mortality but no significance could be found. Overall mortality rate was 7.46%. Malignant neoplasia was the main cause of mortality, accounting for 60% of deaths.

Conclusion: FAP is a rare pathology in our country. Genetic counseling and proper screening programs are essential tools to early diagnosis and follow-up. Surgery is the most effective treatment and the best option to prevent malignant neoplasia.

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Características clínicas e epidemiológicas da polipose adenomatosa familiar em Ribeirão Preto

Palavras-chave:
Polipose adenomatosa familiar
Câncer colorretal
Bolsa ileal

RESUMO

Objetivo: analisar 75 pacientes com polipose adenomatosa familiar (PAF) tratados no Hospital das clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, entre janeiro de 1981 a dezembro de 2011.

Materiais e métodos: trata-se de estudo retrospectivo com coleta dos seguintes dados: sexo, idade, sintomas principais, história familiar, presença de malignidade, cirurgia realizada, morbidade e mortalidade cirúrgicas e fatores relacionados à qualidade de vida.

Resultados: a idade média encontrada foi de 29 anos. A razão entre os sexos foi de 1,2:1 com predomínio no sexo masculino. Sangramento intestinal foi o sintoma mais comum (62,7%). A incidência de câncer colorretal foi de 25,3% (n = 19). Neoplasias extracolônicas foram diagnosticadas em 8% dos pacientes. Colectomia total com íleo-reto anastomose (IRA) foi realizada em 72% (n = 54) dos pacientes. Proctocolectomia com anastomose ileoanal e bolsa ileal em "J" foi realizada em 24% (n = 18) dos casos e em 4% (n=3) dos pacientes optou-se pela proctocolectomia com ileostomia terminal (PCI). As taxas de complicações precoces e tardias foram semelhantes (22,7% × 24%). A cirurgia de bolsa ileal apresentou tendência a maior morbimortalidade, porém sem relevância estatística. A taxa geral de mortalidade foi de 7,46%. Neoplasias malignas foram responsáveis por 60% dos óbitos e complicações cirúrgicas por 40%.

Conclusões: a PAF é uma patologia de baixa incidência no nosso país. O aconselhamento genético e o rastreamento familiar são instrumentos essenciais para o diagnóstico precoce e seguimento adequado. A cirurgia persiste como melhor opção para prevenção do câncer colorretal e tratamento da doença

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant genetic syndrome first described in 1721 by Menzelio.[1] It is the result of a germline mutation in the adenomatous polyposis coli (APC) gene located in chromosome 5q21 responsible for cell growth and apoptosis regulation.[2] In its classical phenotype, patients develop hundreds to a thousand adenomatous polyps between the second and third decades of life.[3] There is also a milder form of the disease called attenuated FAP (AFAP) with fewer polyps throughout the colon. Both exhibit precancerous nature and, without proper treatment, degeneration to colorectal carcinoma (CRC) is inexorable by the fifth to sixth decades of life. There are no studies regarding the incidence of FAP in our country but worldwide incidence is considered the same and estimated at one in every 5,000-10,000 live births.[4]

Family history is of great importance for diagnosis because most patients are asymptomatic or present with nonspecific symptoms such as intestinal bleeding, abdominal pain or changes in bowel habit.[5] FAP may also present with other complications such as desmoid tumors, adenocarcinoma of the small bowel, thyroid cancer, medulloblastomas and osteomas.[6-8]

Surveillance of patients leads to a reduction in CRC-related mortality.[9,10] Individuals with a positive family history should begin annual colon evaluation (i.e. sigmoidoscopy or colonoscopy) by 10-12 years of age.[11] Genetic tests are useful to confirm an APC gene mutation. Once the mutation is discovered in an individual, genetic testing can help identify affected members of the same family.

Surgery is the definitive treatment and options include proctocolectomy with terminal ileostomy (PCI), colectomy with ileorectal anastomosis (IRA) and proctocolectomy with ileal pouch anal anastomosis, also known as restorative proctocolectomy (RCP). Both the patient and the physician have to solve the dilemma of neoplasia control and functional compromise to choose the right procedure. General agreement is that the surgeon must always consider the individual characteristics of each patient.

The aim of this study is to describe the epidemiologic and clinical characteristics, as well as evaluate the outcome of a group of FAP patients treated in our institution.

Metodology

This is a retrospective study of medical records of 75 patients with FAP. All patients were operated in Ribeirão Preto Medical School, University of São Paulo (USP), during the period of January 1981 to December 2011. The following data were collected: gender, age, main symptoms, upper gastrointestinal endoscopy findings, family history, colonic and extra-colonic malignant neoplasia, type of surgery, surgical morbidity and mortality, overall mortality. Factors related to life quality such as sexual dysfunction, bowel habit and fecal continence were also considered. Statistical analysis was performed with GraphPad 5.0 software program. Results of the two main surgical options were compared using Fisher's exact test.

Results

The present study included 75 patients. Average age was 29 years (8 months-60 years) and men [41 (54.7%)] prevailed over women [34 (45.3%)]. The most common symptoms were intestinal bleeding (62.7%), abdominal pain (40%), change in bowel habits (30%) and weight loss (14.7%). We discovered that sixty patients (80%) had other members of the family affected by FAP. Adenomatous polyps were found by upper gastrointestinal endoscopy in 24 (32%) individuals, most of them in the stomach (75%).

CRC incidence was 25.3% (11 men and 8 women) and the average age of this group was 40.9 years old (22-59 years) [Fig. 1]. The diagnosis was made preoperatively in 73.7%, during the surgery in 10.5% and during the follow-up in 15.8% of the cases.

The incidence of extra-colonic neoplasia was 8% (4 desmoid tumors, 1 duodenal adenocarcinoma and 1 thyroid cancer).

Regarding the treatment, IRA was performed in 54 (72%) patients. Eighteen (24%) patients were submitted to RCP and 3 (4%) undergone PCI. The overall early and late post-operative complication rates were similar [22.7% (17 patients)] × [24% (18 patients), respectively]. We noticed a tendency of higher percentage rates of morbidity and mortality for RCP but no significance was found (Tables 1, 2 and 3).

The incidence of diarrhea and use of antidiarrheal agents after RCP was 33.3%. Reported incidence of fecal incontinence was 5%. The rate of diarrhea requiring pharmacologic treatment after IRA was 11% and no fecal incontinence was reported. Sexual dysfunction was noted only after IPAA in a rate of 11%. Rectal cancer incidence after IRA was 3.7% (2 patients).

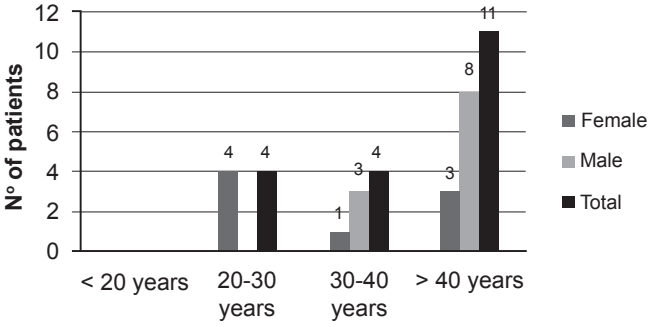

Fig. 1 – Gender and age distribution of colonic adenocarcinomas.

Table 1 – Early and late post-operative complications.

Complications			
Early	(%)	Late	(%)
Anastomotic leak	52.6	Obstruction	42.2
Abdominal abscess	21	Wound complications	15.8
Obstruction	15.8	Retrograde ejaculation	10.5
Pancreatitis	5.3	Fistulae	10.5
GI Bleeding	5.3	DVT	10.5
Wound complications	0	Stenosis	10.5

Table 2 – Morbidity and mortality × surgical procedure.

Surgery	Early complications (%)	Late complications (%)	Mortality (%)
IRA	22.2	20.4	3.7%
RCP	38.9	27.8	5.55%
PCI	0	0	0

IRA, colectomy with ileorectal anastomosis; RCP, restorative proctocolectomy; PCI, proctocolectomy with terminal ileostomy.

Table 3 – Surgical outcomes.

Surgical outcome	IRA	RCP	P-value
Early morbidity	12 (22.2%)	7 (38.9%)	0.2181
Late morbidity	11 (20.4%)	6 (33.3%)	0.3379
Refractory diarrhea	6 (11.1%)	6 (33.3%)	0.0611
Follow-up cancer	2 (3.7%)	1 (5.55%)	1.00
Mortality	1 (1.85%)	1 (5.55%)	0.4401

IRA, colectomy with ileorectal anastomosis; RCP, restorative proctocolectomy, PCI, proctocolectomy with terminal ileostomy.

The cancer incidence after IPAA was 5.5% (one patient developed cuff adenocarcinoma).

Loss to follow-up rate was 10.7%. The maximum follow-up time was 29 years. Overall mortality rate was 7.46% (5 patients). Advanced malignant neoplasia was the main cause of death [60% (3 patients)] and surgical complications (hypovolemic shock and necrohemorrhagic pancreatitis) accounted for the rest.

Discussion

The development of adenomas in FAP precedes symptoms and the disease remains silent for a long period of time. The Danish Polyposis Register analyzed the course of the disease and found a median age at diagnosis of FAP of 19 years.[12] The present study found a higher mean age at diagnosis (29 years) that could be explained by the lack of compliance of screening programs, difficult access to healthcare and medical or patient's negligence.

The symptoms presented by the patients were intestinal bleeding (62.7%), abdominal pain (40%), change in bowel habits (30%) and weight loss (14.7). We found that 42.7% of the patients were asymptomatic and FAP was diagnosed during screening of relatives.

Esophagogastroduodenoscopy helps the detection of gastric, duodenal and periampullary adenomas. Upper gastrointestinal cancer incidence in FAP is higher than general population but rare before the age of 30 years.[13-15] General consensus recommends endoscopic surveillance starting from 25-30 years of age, at intervals of 1-5 years depending on the severity of the disease.[16] The incidence of gastric and duodenal polyps in our study was 24% and 12% respectively. Adenocarcinoma of duodenum was diagnosed in one (1.3%) patient.

Colorectal carcinoma is the main cause of death among patients with FAP. Most patients develop cancer by the age of

39, thus making it important to evaluate the entire colon and to adhere the surveillance program.[5,17] CRC was found in 19 (25.3%) patients in the present study (Fig. 2). The diagnosis was made pre-operatively in 73.7% of the cases during colonoscopy.

Desmoid tumor is a benign neoplasia and the most important extracolonic manifestation of FAP. It has an infiltrative growth pattern and a high recurrence rate after resection. Such aggressive behavior makes this neoplasia the second most common cause of death in FAP. Leal *et al.* found an incidence of 13.2% in a series of 68 patients with no recurrence in a mean follow-up time of 63.1 months after treatment.[18] Another national registry reported an incidence of 11.9% in 55 patients with 28.5% death rate.[6] An English series of 88 patients reported a cure rate of only 14% and deaths in 13% of the cases.[19] The incidence of desmoid tumors in our study was 5.3% (4 patients). Half of the cases was located in the abdominal wall and the other half inside the abdominal cavity. Curative resection was possible in three patients (75%) and no recurrences were noted. No deaths were attributed to this neoplasia (Fig. 3).

Surgery is the most effective treatment option and controversies regarding the best procedure still exist mainly because the choice depends on several factors such as age of the patient, sphincter function, mutation locus, number and site of the polyps, cancer association, patients' commitment to long-term follow-up, and experience of the surgeon. There are no guidelines regarding the optimal timing of operation and most patients undergo surgery between 15-25 years of age.

Most patients in our study (54 [72%]) underwent IRA. IRA is technically simpler than RCP with lower morbidity and mortality rates. It also avoids the need for a permanent ileal stoma seen in PCI, with better quality of life.[20,21] The main advantage of rectal preservation is better functional outcomes. Disadvantages are the need of periodic rectal surveillance for new polyps and the association to metachronous rectal cancer in some cases. It is usually recommended when there are very few polyps in the rectum (less than 20) and in patients with mild genotype.[22,23] In the present study early and late complication rates were similar (22.2% × 20.4%). The main cause of early morbidity was anastomotic dehiscence (41.7%) and the most common late complication was intestinal obstruction (63.7%). Mortality rate related to the procedure was 1.85%.

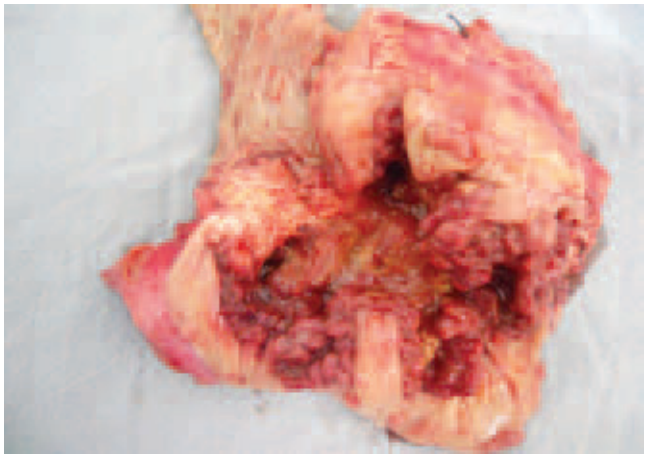

Fig. 2 – Invasive colorectal carcinoma in a patient with FAP.

Fig. 3 – Desmoid tumor of the abdominal wall.

Proctocolectomy with J-pouch ileoanal anastomosis is the gold standard treatment for FAP and was performed in 18 (24%) of the patients. This procedure is typically recommended when there are many polyps in the rectum or in patients with severe genotype (i.e. mutations between codons 1250 and 1464).[20,24,25] Young women considering pregnancy should avoid or postpone RCP as fertility may be reduced as reported in some studies,[26] although a more recent one found no association with the type of operation.[27] Early and late complications rates in our patients were 38.9% and 27.8%. Anastomotic dehiscence was the most common cause of morbidity (71.4%). Mortality rate was 5.5%.

We compared the outcomes of RCP x IRA and found no statistical difference in the rates of diarrhea requiring therapy, early and late complications, mortality and cancer incidence during follow-up.

Aziz *et al.* published a meta-analysis of studies that compared RCP and IRA in 1002 patients.[28] They found that bowel frequency, night defecation and use of incontinence pads were significantly less in the IRA group. They also noted that reoperation within 30 days was more common after ileal pouch construction. No significant differences between the techniques in terms of sexual dysfunction, dietary restriction, or postoperative complications were noted. Rectal cancer was a diagnosis only in the ileorectal group. They concluded that both options have their merits.

Proctocolectomy with terminal ileostomy is the least performed operation. Although very few complications are noted, the need of a permanent stoma may be considered unacceptable by young patients. It was performed in only 3% of the patients and no major complications were noted. There were no deaths in this subgroup.

Conclusion

FAP is an uncommon disease that affects young people culminating with malignant neoplasia if untreated. Specialized centers are required to treat and follow this condition since it demands a multidisciplinary approach. Surgery is the definitive treatment and data concerning FAP in our country is scarce, compromising a better understanding of the epidemi-

ology, clinical aspects and treatment outcomes. We believe that a national registry should ameliorate the problem and improve medical care.

Conflicts of interest

The authors declare no conflicts of interest.

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