*Case report***Familial juvenile polyposis coli; increased risk of colorectal cancer**

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SUMMARY Six patients from one family and one solitary patient with juvenile polyposis coli are described. The histological changes in colonic polyps formed a spectrum from juvenile polyps, through focal to extensive adenomatous change, to adenocarcinomas. One patient aged 49 years had an adenocarcinoma of the colon and in another, aged 33, with rectal polyps and metastatic cancer this was suspected although the primary tumour was not located. Two additional patients, aged 19 and 41 years, had severe adenomatous dysplasia in a juvenile polyp. Four patients also had gastroduodenal polyps. The present findings clearly contradict the previous view that juvenile polyposis coli is not premalignant and only rarely needs surgical treatment. As other recent reports also describe frequent occurrence of neoplastic changes in juvenile polyps, colectomy, and ileorectostomy at the age of about 20 years is recommended as the treatment of choice for juvenile polyposis coli, as in patients with familial adenomatosis coli. Follow up should ideally include gastroduodenoscopy and inspection of the rectal remnant at regular intervals.

Juvenile polyposis coli was recognised only recently as a distinct disease entity.¹ The polyps in juvenile polyposis coli are histologically different from those in familial adenomatosis coli and are fewer in number and manifested earlier.¹⁻⁴ Features in common to both conditions are polypous involvement of the gastrointestinal tract elsewhere than in the colon and autosomal dominant inheritance.¹⁻⁶

Juvenile polyps have been regarded as non-neoplastic hamartomatous lesions with no malignant potential.¹⁻⁶ Treatment has been deemed necessary only for complications, such as bleeding or intussusception.¹⁻⁷ Several reports, however, describe atypical histological patterns in juvenile polyposis coli showing varying degrees of adenomatous features in juvenile polyps and even definite adenocarcinomas.^{2-3, 5, 8-15} Furthermore, the family histories of some juvenile polyposis coli patients reveal an increased incidence of colorectal cancer.^{1-3, 5, 8, 14, 16}

The present report describes seven patients with

juvenile polyposis coli detected in an attempt to create a Finnish registry for familial adenomatosis coli. One solitary patient was earlier considered to have colonic adenomatosis, and one juvenile polyposis coli family was revealed after the detection of anaemia and juvenile polyps in an 18 year old boy, whose relatives were then examined. The need for re-evaluation of indications for surgery in juvenile polyposis coli is discussed on the basis of the histological findings in this and other recent reports.

Case reports**CLINICAL FINDINGS***Case 1*

A male patient underwent five operations for colonic polyposis between the ages of 11 and 17 and at 27 years. The first symptom was chronic obstruction because of caecocolonic intussusception. Altogether 50 polyps, predominantly in the right hemicolon, were removed, on the first two occasions by local excisions, then, after recurrent rectal bleeding and anaemia, by two separate

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Received for publication 2 September 1983

segmental resections, until finally total colectomy with ileorectostomy was performed. Small duodenal and ileal polyps were also found in later endoscopies. The patient is well, now 34 years old, and comes to yearly endoscopic check-ups.

His parents, son, and seven siblings have not had signs of polyposis though six of the latter have been adequately examined. His daughter died perinatally and had had anaemia and rectal bleeding. The cause of death was asphyxia but the colon was not examined at the necropsy.

Cases 2-7

The propositus of the family (II/1, Fig. 1) was an 18 year old boy with anaemia owing to occult bleeding. Rectal bleeding had already occurred when he was 3 years old. Double contrast colography and rectoscopy revealed a number of polyps throughout the colon. Colectomy with ileorectostomy was performed in May 1982 (Fig. 2). His father (I/4) had undergone partial gastrectomy for benign gastric polyps in 1975. He was reexamined with the finding of several polyps up to 5 cm in diameter in the caecum and transverse colon. Although asymptomatic, he underwent the same operation as his son. Altogether, 15 colonic polyps and, in addition, massive gastric polyposis were detected.

While the father and son were in hospital, the 14 year old daughter (II/2) suddenly had rectal bleeding. More than 50 polyps were found in subsequent colography and colonoscopy. The biggest five polyps, up to 4 cm in diameter, were removed by snaring.

Examination of the pedigree revealed three additional patients. An asymptomatic man, aged 52 years (I/1), had a few polyps at colography. As they could not easily be removed by colonoscopy, colectomy with ileorectostomy was undertaken in September 1982. In addition to eight colonic polyps abundant gastric polyposis was also detected. His brother, aged 49 years (I/2), had undergone left hemicolectomy in 1981 at another hospital for three big polyps with an invasive adenocarcinoma in one

Fig. 2 Operative specimen in juvenile polyposis coli; colon and upper rectum (case II/1). About 60 polyps. Severe dysplasia in one of the polyps in caecum.

of them. One and a half years later a pulmonary metastasis was removed.

In 1970 their 33 year old sister (I/3) had been operated on in our department for polyps in the gastric antrum (Fig. 3). She also had rectal polyps, but the colon appeared uninvolved at laparotomy, which revealed metastases in lymph nodes beneath the mesenteric trunk, however. The patient died of metastatic cancer half a year later. The parents of the first generation are alive and well, but the maternal grandmother had died of gastric cancer.

Fig. 1 Pedigree of the present juvenile polyposis coli family (arrow: propositus).

HISTOLOGICAL FINDINGS

All histological specimens of the gastrointestinal tract polyps were reexamined and classified. The specimens comprised 48 colorectal polyps from all seven patients and several biopsies of gastroduodenal lesions in four patients. The findings are summarised in Table 1.

Colorectal polyps were divided into four groups: (1) typical juvenile polyps, (2) juvenile polyps with focal adenomatous change, (3) juvenile polyps with

Fig. 3 Resected stomach of patient I/3 with big polyps in antrum showing adenomatous change.

extensive adenomatous change, (4) severe dysplasia or invasive carcinoma in a polyp. There was, of course, overlap between groups 2 and 3. All patients had at least one colorectal polyp of group 1 or 2, and all polyps showed more or less the features of a juvenile polyp, even those with carcinoma or severe dysplasia.

Typical juvenile polyps (Fig. 4) were pedunculated and the larger ones often deeply lobulated. The stroma was abundant, oedematous, and usually contained inflammatory cells. The glands were sparse and some of them cystically dilated, especially in the central part. The glandular epithelium was composed of regular goblet cells with basal nuclei. The surface was usually smooth and covered by simple absorptive cells, but was

often inflamed and ulcerated. Typical juvenile polyps seemed to be more common in younger patients, and were located predominantly in the right hemicolon.

Juvenile polyps with focal adenomatous change (Fig. 5) had the general pattern of juvenile polyps, but the glandular epithelium showed small areas of adenomatous change (mild to moderate dysplasia): an increased number of nuclei, loss of their basal location, and decrease in the mucin content of the cells, sometimes there was also an increase in the occurrence of mitoses. The glands were often more numerous and more closely packed. Adenomatous change was often seen in the periphery of the polyp, and sometimes comprised only a part of one gland.

Polyps with extensive adenomatous change (Fig. 6) showed mild to moderate dysplasia in most glands. The glands were also clearly more numerous and more closely packed than in typical juvenile polyps, and the stroma was sparse. These polyps differed, however, from usual adenomas by also showing areas with oedematous and inflamed stroma and dilated glands. The juvenile features were most pronounced at the base of the polyp making the border with the surrounding mucosa unclear. Extensive adenomatous change was more common in big polyps; the mean diameters of the polyps were 7.1, 10.1, 15.5, and 19.8 mm in groups 1 to 4, respectively. The differences between group 1 and 2 and group 2 and 3 were nearly significant ($p < 0.05$, Student's *t* test).

Three patients had one polyp belonging to group 4, and in one patient a metastatic adenocarcinoma was probably of colonic origin. In cases II/1 and I/4 severe dysplasia occurred in a juvenile polyp with extensive adenomatous change, in the former locally

Table 1 Number and site of different gastrointestinal polyps histologically examined in seven cases of juvenile polyposis coli

Patient (age, yr; sex)	Detected in all	Colorectal polyps				Gastric polyps	Duodenal polyps
		Histological group*					
		I	II	III	IV		
Case 1 (27 M)	50+	1	4	—	—	—	+
Cases 2-7							
I/1 (52 M)	8	1	—	5	—	++	—
I/2 (49 M)	3	—	2	—	1	—	—
I/3 (33 F)	2+	1	—	—	++	+	—
I/4 (41 M)	15	4	3	2	1	++	++
II/1 (19 M)	60+	11	4	1	1	—	—
II/2 (14 F)	50+	2	1	3	—		

* Group I: typical juvenile polyp; II: juvenile polyp with focal adenomatous change; III: juvenile polyp with extensive adenomatous change; IV: severe dysplasia or invasive carcinoma.

† Metastatic adenocarcinoma in lymph nodes.

Fig. 4 (a) Typical juvenile colonic polyp (case II/1). Note another small juvenile polyp on the right (H and E low power). (b) Dilated glands with regular goblet cells having nuclei against the basement membrane (H and E $\times 50$, orig. mag.).

Fig. 5 (a) Juvenile polyp with focal adenomatous change (case I/4). (b) Some glands on left show mild dysplasia (H and E $\times 50$, orig. mag.).

Fig. 6 (a) Juvenile polyp with extensive adenomatous change (case II/1); deeply lobulated general pattern, tightly packed glands, sparse stroma. Some glands cystically dilated (H and E low power). (b) Glands with mild dysplasia; increased number of nuclei, loss of their basal location and decreased mucin content (H and E $\times 100$, orig. mag.).

and in the latter the change invaded into but not through the muscularis mucosae (Fig. 7). Patient I/2 had an ulcerous partly polypoid adenocarcinoma 3.5 cm in diameter invading the serosa. The other border of the tumour comprised a juvenile polyp with extensive adenomatous change (Fig. 8). Two of the three lesions described above were located in the splenic flexure and one in the caecum.

The primary tumour of the fourth patient (I/3), who had a metastatic, poorly differentiated adenocarcinoma in mesenteric (or subpyloric) lymph nodes, remained undetected. A gastric carcinoma was originally suspected, but the gastric polyps examined (Figs 3, 10) showed no malignant features; so, a colonic origin was probable.

Gastroduodenal polyps were found in four patients out of six examined in this respect. The gastric polyps had the structure of hyperplastic polyps with tortuous glands embedded in an oedematous lamina propria, often with inflammatory cells. In some polyps the glands were dilated as in juvenile polyps (Fig. 9), and in the largest ones deep lobulation was observed. Adenomatous change was seen in case I/3 only (Fig. 10).

The duodenal lesions of two patients showed

hyperplastic features in one, while they appeared as usual tubular adenomas in the other (I/4). The ileal polyps of two patients showed lymphatic hyperplasia histologically.

Fig. 7 Severe dysplasia in juvenile polyp (case I/4); it invaded into muscularis mucosae in the stalk of the polyp (H and E $\times 100$, orig. mag.).

Fig. 8 (a) Carcinoma invading under juvenile polyp (case I/2) (H and E low power). (b) High power view (H and E $\times 100$, orig. mag.).

Discussion

The four juvenile polyposis coli patients with adenocarcinoma or severe dysplasia in a polyp and belonging to one family represent an unusually high frequency of carcinomatous change compared with earlier reports. Although in two of them the change, according to present terminology, could be classified only as severe dysplasia and not as invasive carcinoma, these changes represent irreversible local carcinomatous lesions, which must necessarily be removed. Table 2 summarises the 18 previously reported juvenile polyposis coli families including a few solitary cases.^{1-3 5 8 10-12 14-20} Nine juvenile polyposis coli patients with colorectal adenocarcinoma have now been described, representing 9% of the patients collected here. The mean age of these patients is 40 years (range 23-60 years). A

family history of gastrointestinal cancer was present in at least 12 families, and in some it was very strong.^{1 2}

The histological analysis of colonic polyps in the present series revealed a complete spectrum from non-neoplastic lesions to invasive adenocarcinoma. Typical juvenile polyps were followed by gradually increasing adenomatous changes in polyps, and finally by severe dysplasia and invasive carcinoma. This successive pattern in different polyps strongly suggests that the adenomatous changes and carcinomas in juvenile polyposis coli develop from juvenile polyps. Both polyps with extensive adenomatous change and severe dysplasia or carcinoma retained some juvenile features – for example, dilated glands, stromal oedema, diffuse border with normal epithelium, and deep lobulation.

The hypothesis of a pathogenetic sequence from

Fig. 9 Hyperplastic gastric polyp (case I/4) with tortuous and dilated glands and oedematous stroma with inflammation. Glands are lined by regular surface epithelium (H and E low power).

Fig. 10 Hyperplastic gastric polyp with adenomatous change (patient I/3). In addition to regular epithelium there are glands with dysplastic change (H and E $\times 50$, orig. mag.).

Table 2 Occurrence of colorectal and other gastrointestinal tract cancer in juvenile polyposis coli patients and their families

	Families	Solitary cases	Cases in total	Patients with colon cancer (age)	Family history of gastrointestinal tract cancer (no)
Horrilleno <i>et al</i> (1957) ¹⁶	1	—	1	—	+ (1)
Veale <i>et al</i> (1966) ¹	2	9	11	—	+ (14)
Smilow <i>et al</i> (1966) ¹⁷	1	—	3	1 (60)	—
Haggitt <i>et al</i> (1970) ⁸	1	—	2	—	+ (2)
Sachatello <i>et al</i> (1970) ¹⁸	1	—	3	—	—
Gathright <i>et al</i> (1974) ¹⁹	2	—	10	—	—
Stemper <i>et al</i> (1975) ²	1	—	12	2 (30, 45)	+ (9)
Velcek <i>et al</i> (1976) ¹⁰	1	—	2	—	—
Restrepo <i>et al</i> (1978) ³	5	14	27	1 (40)	+ (2)
Goodman <i>et al</i> (1979) ¹²	—	1	1	1 (23)	—
Grigioni <i>et al</i> (1981) ¹⁴	1	1	2	1 (25)	+ (2)
Grotsky <i>et al</i> (1982) ⁵	1	—	19	—	+ (2)
Rozen <i>et al</i> (1982) ²⁰	1	—	2	1 (58)	—
Present series	1	1	7	2 (33, 49)	+ (1)
	19	26	102	9	(33)

juvenile polyps to adenomas, presented recently,^{12 14} is supported by the present findings. In fact, most cases of juvenile polyposis coli seem to have a similar spectrum of histological features starting from juvenile or hyperplastic polyps.^{1-3 5 8-15} Thus juvenile polyps and possibly also hyperplastic polyps,¹⁴ usually regarded as non-neoplastic lesions, seem to have a certain pre-malignant potential, although less so than adenomas. As our young patients clearly had more colonic polyps, especially of the typical juvenile type, and older patients less polyps but more often with extensive adenomatous change, it is likely that only a few juvenile polyps progress to adenoma, while most of them regress with time. A similar phenomenon has been suggested to occur in the general population, where the hyperplastic polyps might represent a reservoir, from which adenomas originate.¹⁴

As in familial adenomatosis coli in juvenile polyposis coli upper gastrointestinal tract polyps occur commonly, but gastroduodenal adenomas seem to be more frequent in the former.²¹ In this respect also, the genetically determined factor in juvenile polyposis coli, responsible for the development of polyps, seems to be weaker than in familial adenomatosis. It is interesting that the non-neoplastic fundic gland polyps characteristic of familial adenomatosis,²² and the gastric lesions of the present patients had similar features and also resembled colonic juvenile polyps. Examination and follow up of gastroduodenal lesions in juvenile polyposis coli may also be of value.

In earlier reports of juvenile polyposis coli the authors considered surgical treatment as indicated only in cases with severe symptoms and warned of prophylactic surgery for fear of malignancy.^{8 10 18 19} Although adenomatous change in juvenile polyps seems to be more the rule than the exception, most authors still emphasise only the need for follow up.^{5 11 13 15} Velcek *et al.*¹⁰ however, observed that more than 80% of children with diffuse juvenile polyposis underwent colectomy. In our view, the evidence of an increased risk of cancer in juvenile polyposis coli is sufficient for recommending colectomy with ileorectostomy and regular check up of the remaining rectum and the upper gastrointestinal tract. The optimal time for the operation may be at 20 years of age as in familial adenomatosis, considering the age of occurrence of cancer in the cases reported. It is clear that in patients with only a few juvenile polyps colonoscopic polypectomies may offer a reasonable alternative, but this requires regular colonoscopic follow up. The need to examine the relatives is also emphasised.

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