0021-972X/95/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 80, No. 10
Printed in U.S.A.

The Prevalence of Colonic Polyps in Acromegaly: A Colonoscopic and Pathological Study in 103 Patients

BERNARD DELHOUGNE, CATHERINE DENEUX, ROGER ABS, PHILIPPE CHANSON, HERBERT FIERENS, PATRICK LAURENT-PUIG, IVO DUYSBURGH, ACHILLE STEVENAERT, ANTOINE TABARIN, JEAN DELWAIDE, GILBERT SCHAISON, JACQUES BELAÏCHE, AND ALBERT BECKERS

Departments of Gastroenterology (B.D., J.D., J.B.), Neurosurgery (A.S.), and Endocrinology (A.B.), University of Liège, Liège, Belgium; Departments of Gastroenterology (C.D., P.L.-P.) and Endocrinology (P.C., G.S.), University of Paris, Paris, France; Departments of Endocrinology (R.A.) and Gastroenterology (H.F., I.D.), University of Antwerp, Antwerp, Belgium; and the Department of Endocrinology, University of Bordeaux (A.T.), Bordeaux, France

ABSTRACT

Patients with acromegaly are reported to be at risk of developing adenomatous colonic polyps, which are considered to be preneoplastic lesions. This assumption is, however, usually drawn from results obtained in rather small series of patients or without a control group. We, therefore, undertook a prospective colonoscopic and pathological study comprising 103 acromegalic patients and 138 nonacromegalic control subjects referred for irritable bowel syndrome.

The prevalence of adenomatous colonic polyps was significantly increased in acromegalic patients compared to that in control subjects (22.3% *vs.* 8.0%; $P = 0.0024$). The significance was similarly present in male acromegalic patients (28.6% *vs.* 5.5% in male control subjects; $P = 0.0026$), but was absent in female acromegalic patients. The prevalence of colonic polyps was also significantly increased in the group of acromegalic patients under 55 yr of age (20.0% *vs.* 3.0% in the control group of the same age; $P = 0.0026$). Other characteristics of adenomatous colonic polyps in acromegaly were the multiplicity and the presence proximal to the splenic flexure. No difference in the duration of acromegaly was found between patients with or without adenomatous polyps. The prevalence of hyperplastic colonic polyps was also significantly increased to 24.3% in acromegalic patients *vs* 4.4% in control subjects ($P < 0.001$). In conclusion, in view of the increased incidence of adenomatous colonic polyps, colonoscopy should be part of the follow-up examinations in acromegaly. (*J Clin Endocrinol Metab* **80:** 3223–3226, 1995)

PATIENTS with acromegaly are known to have a reduced life expectancy (1, 2). The main causes of this increased mortality are of cardiovascular and tumoral origin. Neoplastic disorders are encountered three times as frequently in acromegalic patients as in a normal population (3, 4). Recently, several studies reported an increased prevalence of colonic polyps in acromegaly (1, 5–15). As adenomatous colonic polyps are considered to represent a preneoplasic lesion, precocious diagnosis is of primordial interest to prevent further degeneration into a colonic carcinoma. The value of the earlier prospective studies is restricted by the limited number of patients. A prospective colonoscopy was performed in our acromegalic patients, and a pathological examination of the resected polyps was carried out. We report here the results obtained in 103 acromegalic patients and compare the findings with those gathered in 138 patients with functional colonopathy.

Subjects and Methods

A total of 103 acromegalic patients (male/female ratio, 49/54; mean age ± SD, 51 ± 12 yr) were studied in four endocrinological centers: CHU Liege, Hôpital Bicêtre Paris, UZ Antwerp, and CHU Bordeaux. Diagnosis of acromegaly had been suspected by the clinical presentation. It was subsequently confirmed by the finding of elevated plasma concentrations of GH and insulin-like growth factor I (IGF-I), radiological demonstration of a pituitary adenoma, and, in some patients, positive immunocytochemical examination of the resected pituitary tissue. The interval between the onset of symptoms of acromegaly and colonoscopy was calculated as the duration of the disease. Acromegaly was part of the multiple endocrine neoplasia type 1 syndrome in two patients. Two other acromegalics belonged to the same fratria and probably represented familial acromegaly. Two acromegalics had a previous history of colonic polyps, and seven had a positive family history for colonic polyps. The patients were declared cured after neurosurgery when plasma GH suppression below 2 μg/L after a glucose load and normal plasma IGF-I levels were found. They were considered stabilized when the plasma IGF-I level was normalized during somatostatin analog treatment.

The control group consisted of 138 patients (male/female ratio, 55/83; mean age ± SD, 53 ± 15 yr), who were investigated at the Department of Gastroenterology of the CHU Liege for symptoms evoking irritable bowel syndrome, such as chronic constipation, diarrhea, or atypical abdominal pain. The screening program consisted of a colonoscopy. When found, the polyps were removed and examined histologically. The statistical analyses were performed with the Fisher test, and $P \leq 0.05$ was considered significant.

Received February 1, 1995. Revision received June 28, 1995. Accepted July 7, 1995.

Address all correspondence and requests for reprints to: Dr. A. Beckers, CHU Liège, Department of Endocrinology, B-4000 Liege, Belgium.

Results

There was a significant increase in adenomatous colonic polyps in the acromegalic group relative to that in the control group, with a prevalence of 23 of 103 (22.3%) *vs.* 11 of 138

(8.0%; $P = 0.0024$). In the male acromegalics, 14 of 49 (28.6%) had adenomatous polyps *vs.* 3 of 55 (5.5%) in the male controls ($P = 0.0026$). There was no statistically significant difference in the frequency of colonic polyps between the female populations (9 of 54 acromegalics (16.7%) *vs.* 8 of 83 controls; 9.6%; $P = 0.2899$). Multiple adenomatous polyps were found in 6 acromegalic patients but in none of the control subjects. In both groups, all polyps, except 5 in the acromegalic group, were distal to the splenic flexure. The prevalence of colonic polyps was high in acromegalics under 55 yr of age [14 of 70 (20.0%) *vs.* 2 of 66 (3.0%) in controls under 55 yr of age; $P = 0.0026$]. The prevalence of colonic polyps was also elevated in acromegalics above 55 yr of age, but the difference from controls was not statistically significant [9 of 33 (27.3%) *vs.* 9 of 72 (12.5%); $P = 0.0635$]. There was no statistically significant difference between the mean age of acromegalic patients with and that of those without adenomatous polyps (54.9 ± 10.6 yr *vs.* 50.2 ± 11.4 yr; $P = 0.0853$). There was a statistically significant difference in the mean age of control subjects with or without adenomatous polyps (61.8 ± 16.1 yr *vs.* 52.4 ± 14.2 yr; $P = 0.0434$). There was no statistically significant difference between the mean age of acromegalic patients with adenomatous polyps and that of control subjects with adenomatous polyps (54.9 ± 10.6 yr *vs.* 61.8 ± 11.9 yr; $P = 0.1530$). There was no difference in duration of the disease between acromegalic patients with or without adenomatous polyps (69 *vs.* 80 months; $P = 0.5140$).

At the time of colonoscopy, 50 of 103 acromegalic patients showed active disease. Eleven of these patients had at least 1 polyp (22.0%) *vs.* 12/53 acromegalics (22.6%) considered stabilized or cured ($P = 1$). No adenocarcinoma was incidentally discovered. Neither of the 2 patients with a familial history for acromegaly had colonic polyps. One of the 7 acromegalic patients with a family history for colonic cancer had colonic polyps. Hyperplastic polyps were found in 25 of 103 acromegalics (24.3%) and in 6 of 138 controls (4.4%; $P < 0.001$). Three acromegalic patients had both adenomatous and hyperplastic polyps. A review of the results is given in Table 1.

Colonoscopy was complete by reaching the cecum in 86 of 103 (83.5%) of the acromegalic patients *vs.* 125 of 138 (90.6%) of the control subjects ($P = 0.1165$). The mean age and sex ratio of acromegalic patients and control subjects were statistically not different.

TABLE 1. Colonic polyps in acromegalic patients *vs.* control subjects

	Acromegalic group	Control group	*P*
Adenomatous polyps	23/103 (22.3)	11/138 (8)	0.0024
Multiple adenomatous polyps	6/103 (5.8)	0/138 (0)	
Males with adenomatous polyps	14/49 (28.6)	3/55 (5.5)	0.0026
Females with adenomatous polyps	9/54 (16.7)	8/83 (9.6)	0.2899
<55 yr old with adenomatous polyps	14/70 (20.0)	2/66 (3.0)	0.0026
>55 yr old with adenomatous polyps	9/33 (27.3)	9/72 (12.5)	0.0635
Hyperplastic polyps	25/103 (24.3)	6/138 (4.4)	<0.001

Percentages are given in *parentheses.*

Discussion

Acromegaly is a rare disease with an incidence of 3/million. The life expectancy of an acromegalic patient is reduced compared to that of a normal individual. Earlier reports mention mortality occurring in 26–50% of patients before the age of 50 yr (1, 2). More recently, probably influenced by a more adequate therapeutical approach, the mortality rate was reported to be 16% at the age of 50 yr and 29% at the age of 60 yr, respectively (3). Cardiovascular complications, specifically cardiomyopathy and cerebral vascular accidents, remain the main cause of death in acromegalic patients (16). The second most common reason for mortality is the development of neoplastic disorders. The global risk of an acromegalic patient to present with a carcinoma was estimated to be 3 times higher than that for a normal individual (3). On a cohort of 1000 acromegalic patients, the risk of tumoral development in acromegaly was increased by 60% compared to that in a control population (13). In another study, however, the increased carcinogenic risk was only observed in the male acromegalic patients (17). When comparing a group of 87 acromegalic patients with a group of about 200 patients with other pituitary tumors, the former group showed a 2.5 times increase in neoplasia as well as a more frequent occurrence of benign tumors (4).

Recently, several studies have also indicated an increased prevalence of adenomatous colonic polyps. To our knowledge, in 7 prospective reports a systematic search for polyps by colonoscopy was undertaken, but only that by Vasen *et al.* included a control group (6, 11–15, 18). In our study, 30 adenomatous polyps, amounting to 22.3% of the patients, were resected. This prevalence exceeds significantly the 8.0% of adenomatous polyps found in the control population. Brunner *et al.* found 4 adenomatous polyps in a group of 29 acromegalic patients (13.8%), with an increased prevalence in the male acromegalics, in accordance with our findings of a male predominance (11). Klein *et al.* (6) recorded a prevalence of adenomatous polyps of 29.4%, but in a smaller series of 17 acromegalic patients. No difference in age was apparent between this and our group of acromegalics. It is unlikely that environmental factor differences between the European and the Pennsylvanian population could explain this large difference in prevalence. In the series of Ezzat *et al.* (12), revealing a prevalence of 34.7% of adenomatous polyps, colonoscopy was performed in patients with an active form of acromegaly, whereas some of our patients showed stabilized or cured acromegaly. In another study performed in the same conditions of active acromegaly, 13 patients of a total of 20 acromegalics (65.0%) showed the presence of adenomatous polyps (18). The difference in recruitment of the patients, however, may not play a role in the discordant results. It seems unreasonable that a regression of a colonic polyp occurs with the normalization of plasma GH and IGF-I concentrations. Indeed, in our series we did not find a correlation between the level of activity of the acromegaly at the time of colonoscopy and the finding of a polyp. Also, we could not demonstrate a relation between the duration of the acromegaly and the presence of a polyp. The same conclusion was made in the study of Vasen *et al.*, which included

a control group (15). Their prevalence of 22% of colonic polyps is similar to our results.

The prevalence of 8.0% of adenomatous polyps in the control population with a mean age of 53 yr corresponds to the expected prevalence in the age group. Raymond *et al.* (18) discovered an incidence of 11% of adenomatous polyps in a population selected on the basis of functional colonopathy and reported an incidence of 9.6% at the age of 50 yr at autopsy examination. Recently, a study evaluated the results of colonoscopy performed in 210 individuals without abdominal complaints (19). It showed an incidence of 11.2% of adenomas in the age group of 50–54 yr.

Colonoscopy in acromegalic patients did not permit visualization of the cecum in 16.5%. The difficulty performing a complete colonoscopy is caused by the higher frequency of a dolichocolon in acromegaly. The incomplete examination may be a reason to underestimate the frequency of polyps.

Hyperplastic colonic polyps were detected in 24.3% of the acromegalic patients. These polyps are considered nonneoplastic. A filiation hyperplastic-adenomatous polyp has not been established, but hyperplastic polyps may sometimes comprise adenomatous changes with the possibility of neoplastic degeneration (20). In our series of hyperplastic polyps we did not discover adenomatous alterations. Elevated GH levels could explain hyperplastic polyps in mucosal epithelium, but until now not the development of adenomatous polyps.

Acromegaly is due to an excessive and inadequate production of GH, inducing the hypersecretion of IGF-I. Both hormones are known to promote cellular growth. Several studies indicate a pathogenic role of these growth factors in colonic tumorigenesis. A first argument was found in the studies showing multiorgan neoplastic degeneration in rats injected with GH (21). More recently, it has been shown that GH has the capacity to induce the expression of oncogenes such as c-*myc* in the liver and kidney of mammals (22). Also, *in vitro* GH and IGF-I are capable of initiating cellular proliferation. Furthermore, the presence of IGF-I receptors on pulmonary and colonic tumors has been confirmed (23). Conversely, somatostatin is able to inhibit the cellular growth of some colonic carcinoma cells transplanted into mice (24). Elevated levels of messenger ribonucleic acid for IGF-II were found in colonic carcinoma cells, but the level of IGF-I messenger ribonucleic acid is only slightly increased compared to that in normal colonic cells (25). Recently, an increased mucosal cell proliferation in the sigmoid of acromegalics with active disease was noted, but not in patients with cured disease (26).

The biomolecular approach in determination of the pathogenesis of pituitary adenomas has permitted a spectacular progress during the last years. Several studies support a monoclonal theory for the development of pituitary adenomas (27). The *gsp* oncogene has been identified in about 40% of all somatotrope adenomas that cause acromegaly (28). A mutation within this gene encoding for a Gα protein is responsible for the constitutive stimulation of cAMP, the primary intracellular mediator for the secretion of GH. The gene encoding for the *gsp* oncogene is located on chromosome 20 (29). More recently, the loss of chromosome 11q13 was also detected in some GH-secreting pituitary adenomas (30). This chromosomal band contains the *MEN1* antioncogene, whose deletion is accompanied by the development of the multiple endocrine neoplasia type 1 syndrome. The tumorigenesis of somatotrope adenomas may thus be associated with the mutation of dominant protooncogenes or an inactivation of recessive antioncogenes.

Both of the same mechanisms are implicated in the tumorigenesis of colonic carcinomas. The colonic carcinoma is of monoclonal origin and is induced by the activation of multiple oncogenes and the loss of antioncogenes (31). The *APC* gene (for adenomatous polyposis coli) is located on chromosome 5q21. In 60% of all colonic carcinomas or colonic adenomas, a mutation of the *APC* gene was uncovered (32). In another study, the loss of part of the long arm of chromosome 5 was estimated to be between 5–50% in colonic cancers (33). Another frequent genetic alteration in colonic cancer is activation of the K-*ras* oncogene on the long arm of chromosome 12. In 50% of all carcinomas and adenomas larger than 10 mm, this lesion has been detected (33). No such defect was found in a pituitary adenoma. The loss of the long arm of chromosome 17 is estimated to be 75% in colonic cancer (34). The *p53* antioncogene is located on this chromosome and encodes for a protein inhibiting the replication process in genetically altered cells (35). Another frequent region of deletion is located on chromosome 18q. The *DCC* gene (for deleted in colorectal cancer) that controls the cellular adhesion is lost in 70% of adenomas with severe dysplasia (33, 36). Until now, no alteration in this gene has been found in pituitary adenomas.

In conclusion, our study shows that acromegalic patients are at risk for developing colonic adenomatous polyps. Coloscopic screening will be beneficial for early detection of colonic cancer. Further study is required to determine the pathogenesis, as a genetic event common to acromegaly and colonic polyp has not been discovered until now.

References

1. **Evans HM, Briggs JH, Dixon JS.** 1966 Acromegaly. In: Harris GW, Donovan BT, eds. The pituitary gland. London: Butterworths; 439–469.
2. **Wright AD, Hill DM, Lowly C, Fraser TR.** 1970 Mortality in acromegaly. Q J Med. 39:1–16.
3. **Bengtsson BA, Eden S, Ernest I, Oden A, Sjögren B.** 1988 Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med Scand. 223:327–335.
4. **Barzilay J, Heatley GJ, Cushing GW.** 1991 Benign and malignant tumors in patients with acromegaly. Arch Intern Med. 151:1629–1632.
5. **Capanna R, Gherlinzani F.** 1981 Acromegaly associated with neoplasia. Ital J Orthop Traumatol. 7:123–126.
6. **Klein I, Parveen G, Gravoeler JS, Vanthiel DH.** 1982 Colonic polyps in patients with acromegaly. Ann Intern Med. 97:27–30.
7. **Ituarte EM, Petrini J, Hershman JM.** 1984 Acromegaly and colon cancer. Ann Intern Med. 101:627–628.
8. **Pines A, Rozen P, Ron E, Gilat T.** 1985 Gastrointestinal tumors in acromegalic patients. Am J Gastroenterol. 80:266–269.
9. **Ritter MM, Richter WO, Schwandt P.** 1987 Acromegaly and colon cancer. Ann Intern Med. 106:636–637.
10. **Ziel FH, Peters AL.** 1988 Acromegaly and gastrointestinal adenocarcinomas. Ann Intern Med. 109:514–515.
11. **Brunner JE, Johnson CC, Zafar S, Peterson EL, Brunner JF, Mellinger RC.** 1990 Colon cancer and polyps in acromegaly: increased risk associated with family history of colon cancer. Clin Endocrinol (Oxf). 32:65–71.

12. **Ezzat S, Strom C, Melmed S.** 1991 Colon polyps in acromegaly. Ann Intern Med. 114:754–755.
13. **Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni Jr JF.** 1991 Acromegaly and gastrointestinal cancer. Cancer. 68:1673–1677.
14. **Ladas SD, Thalassinos NC, Ioannides G, Raptis SA.** 1994 Does acromegaly really predispose to an increased prevalence of gastrointestinal tumours? Clin Endocrinol (Oxf). 41:597–601.
15. **Vasen HFA, van Epercum KJ, Roelfsma F, et al.** 1994 Increased prevalence of colonic adenomas in patients with acromegaly. Eur J Endocrinol. 131:235–237.
16. **Rosen T, Bengtsson BA.** 1990 Premature mortality due to cardiovascular disease in hypopituitarism. Lancet. 336:285–288.
17. **Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R.** 1980 Epidemiology of acromegaly in the Newcastle region. Clin Endocrinol (Oxf). 12:71–79.
18. **Raymond JM, Lefort G, Guerin J, et al.** 1989 Significant increase in the prevalence of adenomatous colorectal polyps (ACRP) in acromegalic patients. A series of 20 patients. Gastroenterology. 5:A411.
19. **Rex DK, Lehman GA, Hawes RH, Ulbright TM, Smith JJ.** 1991 Screening colonoscopy in asymptomatic average-risk persons with negative faecal occult blood tests. Gastroenterology. 100:64–67.
20. **Cooper H, Patchefasky AS, Marks G.** 1979 Adenomatous and carcinomatous changes within hyperplastic colonic epithelium. Dis Colon Rectum. 22:152–155.
21. **Moon HD, Simpson ME, Li CH, Evans HM.** 1950 Neoplasma in rats treated with pituitary growth hormone in pulmonary and lymphatic tissues. Cancer Res. 10:297–308.
22. **Murphy LJ, Bell GI, Friesen HG.** 1987 Growth hormone stimulates sequential induction of c-*myc* and insulin-like growth factor I expression *in vivo*. Endocrinology. 120:1806–1812.
23. **Pollack MN, Perdue JF, Margolese RG, Baer K, Richard M.** 1987 Presence of somatomedin receptors on primary human breast and colon carcinomas. Cancer Lett. 38:223–230.
24. **Smith JP, Solomon TE.** 1988 Effects of gastrin, proglumide, and somatostatin on growth of human colon cancer. Gastroenterology. 95:1541–1548.
25. **Tricoli JV, Rall LB, Karakousis CP, et al.** 1986 Enhanced levels of insulin-like growth factor messenger RNA in human colon carcinomas and liposarcomas. Cancer Res. 46:6169–6173.
26. **Cats A, Dullaart RPF, Zwart N, de Vries EGE, Hardonk MJ, Kleibeuker JH.** 1993 Increased epithelial cell proliferation in the colon in patients with acromegaly. Neth J Med. 42:A3.
27. **Herman V, Fagin J, Gonsky R, Kovacs K, Melmed SH.** 1990 Clonal origin of pituitary adenomas. J. Clin Endocrinol Metab. 71:1427–1433.
28. **Vallar L, Spada A, Giannattasio G.** 1987 Altered Gs and adenylate cyclase activity in human GH-secreting pituitary adenomas. Nature. 330:566–568.
29. **Blatt C, Eversole-Cire P, Cohn VH, et al.** 1988 Chromosomal localization of genes encoding guanine nucleotide-binding protein subunits in mouse and human. Proc Natl Acad Sci USA. 85:7642–7646.
30. **Thakker RV, Pook MA, Wooding C, Boscaro M, Scanarini M, Clayton RN.** 1993 Association of somatotrophinomas with loss of alleles on chromosome 11 with *gsp* mutations. J Clin Invest. 92: 2815–2821.
31. **Kinzler KW, Vogelstein B.** 1992 The colorectal cancer gene hunt: current findings. Hosp Pract Off Ed. 15:51–58.
32. **Powell SM, Zilz N, Beazer-Barclay Y, et al.** 1992 APC mutations occur early during colorectal tumorigenesis. Nature. 359:235–237.
33. **Vogelstein B, Fearon ER, Kern SE, et al.** 1989 Allelotype of colorectal carcinomas. Science. 244:207–211.
34. **Delattre O, Olschwang S, Law DJ, et al.** 1989 Multiple genetic alterations in distal and proximal colorectal cancer. Lancet. 2:353–356.
35. **Finlay CA, Hinds PW, Levine AJ.** 1989 The p53 proto-oncogene can act as a suppressor of transformation. Cell. 57:1083–1093.
36. **Fearon ER, Cho KR, Nigro JM, et al.** 1990 Identification of a chromosome 18q gene that is altered in colorectal cancers. Science. 247: 49–56.