Acromegaly Caused by Growth Hormone-relating Hormone in a Patient with Multiple Endocrine Neoplasia Type I

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A 51-year-old Caucasian man with multiple endocrine neoplasia (MEN) type I syndrome presented with clinical features of acromegaly. Exploration of the pituitary gland only revealed somatotrophic hyperplasia and his plasma growth hormone (GH) levels remained elevated. Production of growth hormone-releasing hormone (GHRH) by an ectopic tumor was suspected and, after additional investigations, a large pancreatic tumor was detected and removed. As the pancreatic tail contained multiple (occult) adenomas, lifelong follow-up was considered necessary. The patient has been recurrence-free for 10 years. All 19 living relatives of this patient were analysed for endocrine disorders related to MEN I syndrome. A brother was found to suffer from peptic ulcer disease caused by hyperparathyroidism and, during screening for other organ involvement associated with the MEN I syndrome, two tumors were found, one (4 cm) in the pancreatic tail region and one in the right adrenal gland. To date, six other family members have been found to suffer or have suffered from hyperparathyroidism and in a male subject, a prolactinoma and hyperparathyroidism were detected.

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Introduction

Although acromegaly is generally caused by a growth hormone-secreting pituitary adenoma, it can also be induced by extra-pituitary endocrine tumors that secrete growth hormone-releasing factor.1,2 In 1980, Frohman et al. were the first to report a patient with a pancreatic growth hormone-releasing hormone (GHRH)-producing tumor.3 Subsequent to the isolation and identification of GHRH in 19824,5 and the development of biochemical and immunohistochemical tests for GHRH,6-8 clinical awareness of this cause of acromegaly has increased its recognition.

We report a patient, who belongs to a family with the syndrome of multiple endocrine neoplasia (MEN) type I, who had acromegaly caused by a pancreatic GHRH-producing tumor, and the endocrine disorders found in his relatives. Hitherto, eleven cases of proven GHRH-secreting pancreatic tumors have been described.9-19

Case Reports

Patient A

Patient A, a 51-year-old man, had suffered from renal calculi since 1964 and was found to have hypercalcemia (2.95 mmol/l; normal (N) 2.25–2.55 mmol/l) caused by hyperparathyroidism. There was a positive family history of hyperparathyroidism (one sister) and gastric ulcers (mother and one grandmother). It was noted that he had coarse facial features suggestive of acromegaly. A neck operation for parathyroidectomy was performed in December 1983, during which, an adenoma was found and removed and two normal parathyroids were identified, but the fourth parathyroid could not be located. Postoperatively, hypercalcemia persisted (2.76 mmol/l) and a second neck operation was performed in April 1984, when an enlarged parathyroid gland, histological examination of
which revealed an adeoma, located dorsal to the thyroid was found. After this operation the patient became normocalcemic.

As the patient's acromegaly had progressed, various investigations had been performed to identify its cause. His mean plasma GH levels were elevated on two occasions (13.8 and 23.0 ng/ml; N 0.5–5 ng/ml). A skull x-ray showed no sellar enlargement, but a sellar planigram and CT scan revealed slight asymmetry of the pituitary gland. An ectopic GHRH-producing tumor was suspected and CT scanning of the neck, thorax and abdomen was performed, which showed nothing abnormal.

Treatment was started with bromocriptine, which, unfortunately resulted in no clinical improvement. As the patient's characteristics were consistent with the MEN type I syndrome, his acromegaly was suspected to be caused by a small pituitary adenoma and a transsphenoidal pituitary exploration was performed. Histology of the specimen removed only revealed somatotrophic hyperplasia, a finding that was strongly suggestive of GH overproduction caused by GHRH stimulation. His plasma GH levels were still slightly elevated, but his plasma somatomedins (IGF-I) level was extremely high (74 nmol/l).

Laboratory analysis of immunoreactive (ir) GHRH levels in his plasma confirmed they were raised (3809 ng/l; N 10–60 ng/l). As CT scanning of the hypothalamic region had showed no abnormalities, an ectopic source of GHRH production was sought again. Repeated CT scanning of the abdomen now revealed a tumor, 5 cm in diameter, in the body of the pancreas. This finding was confirmed by magnetic resonance imaging (MRI), selective arteriography and ultrasound. Revision of the first abdominal CT scan performed in 1983 also revealed the tumor.

In April 1985, he underwent a laparotomy and a mass was found close to the head of the pancreas. A subtotal pancreatectomy was performed, leaving the juxta-duodenal part of the pancreatic head in situ. During the operation, venous samples were taken from the splenic and portal circulation and the GHRH levels in the portal venous blood were found to be raised (up to 31118 ng/l).

The operative specimen contained one large (5 cm in diameter) and three small (occult) tumors, which immunohistochemistry confirmed possessed GHRH, but no GH, activity. Postoperatively, the GHRH levels returned to normal (40 ng/l), as did the other test results, and clinically, the patient improved considerably.

At present, this patient has been followed up for 10 years and is still in total remission. In 1988, he developed diabetes mellitus, which has been controlled successfully using oral medication alone. Apart from this, he is healthy and has been cured clinically as well as biochemically of both his hyperparathyroidism and acromegaly.

Patient B

Patient B, the 54-year-old brother of patient A, was investigated in 1988 for upper abdominal discomfort, dyspepsia and early satiety. At the age of 18, he had suffered from a perforated gastric ulcer. Subsequent analysis demonstrated a gastric ulcer associated with hyperparathyroidism, but no other hormonal abnormalities were detected. A CT scan and MRI of his abdomen showed a 3-cm-diameter tumor in the right adrenal gland and one, 4 cm in diameter, in the pancreatic tail. Biochemical screening of both tumors showed they exhibited no endocrine activity. In 1989, a successful subtotal (3.5 glands) parathyroidectomy was performed and the patient became normocalcemic. As his pancreatic and adrenal tumors were asymptomatic, surgery for these adenomas was considered unnecessary, but he was followed up. In 1994, during a routine abdominal CT scan, metastatic nodules were found in his liver. He has been treated with octreotide and the tumor has grown no further at the time of writing.

Patient C

Patient C, a son of patient B, had hyperparathyroidism in combination with elevated plasma prolactin (PRL: 71 μg/l; N<15 μg/l) and low luteinizing hormone (LH: 0.8 U/l; N 3–8 U/l) and follicle-stimulating hormone (FSH: 1.5 U/l; N 2–8 U/l) levels. Administration of thyrotropin-releasing hormone (TRH) did not release any PRL. Only partial release responses of LH and FSH were evoked by luteinizing hormone-releasing hormone (LHRH) administration, but his plasma testosterone level was normal (35.2 nmol/l). MRI of his skull showed an adenoma with minimal suprasellar extension. This patient is now being treated with octahydrobenzol (g) quinoline (Norprolac), a new dopaminergic drug. In 1992, a successful (3.5 glands) parathyroidectomy was performed.

Epilogue

All the other 16 living members of these patients' family were likewise screened for endocrine abnormalities. It also transpired that one of patient A's sisters, who, at the age of 45, died of breast cancer in 1976, had undergone a partial parathyroidectomy in her late twenties. Five other family members had hyperparathyroidism (one became symptomatic with renal calculi during the analysis), but in none of them did radiological examination of the abdomen reveal any abnormalities. All five underwent partial parathyroidectomies which, to date, appear to have
ECTOPIC GHRH-PRODUCING TUMOR IN A MEN I PATIENT

Discussion

The syndrome of MEN type I is an autosomal dominant inherited disease, affecting males and females equally, that can involve the parathyroids, pancreatic islet cells, pituitary and adrenal cortex. It becomes clinically manifest in the third or fourth decade, primary hyperparathyroidism most frequently being the first manifestation. In 90 to 97% of patients, biochemical evidence of hyperparathyroidism is found, whereas pancreatic islet cell neoplasia is found in 30 to 80% and pituitary tumors occur in 15 to 50%.

Hyperparathyroidism, the most common endocrine abnormality in MEN I syndrome, may remain asymptomatic for a long time, but generally precedes the clinical onset of an islet cell or pituitary neoplasm by several years. Symptoms usually consist of renal or ureteral lithiasis or nephrocalcinosis, skeletal manifestations being less common. After subtotal parathyroidectomy (removal of 3.5 glands), the incidence of recurrent hyperparathyroidism has been reported to be as high as 40% and the incidence of permanent hypoparathyroidism is about 25%.

The most common pancreatic islet cell tumor in MEN I syndrome is gastrinoma, which is usually malignant and multicentric. The second most common is insulinoma, which is usually benign, small (less than 1 cm in diameter) and multiple. Other well known pancreatic islet cell neoplasms are glucagonomas and somatostationomas, whereas tumors secreting vasoactive intestinal peptide or glucagonomas and somatostationomas, whereas tumors secreting vasoactive intestinal peptide or pancreatic polypeptide occur less frequently.

Primary pituitary tumors occurring in MEN I syndrome cause symptoms either as a result of hypersecretion of hormones or compression of adjacent structures. Prolactin-secreting micro-adenomas are the most common abnormality. About 30% of patients exhibit acromegaly as a consequence of growth hormone overproduction.

Acromegaly is an uncommon manifestation of MEN I and is usually caused by a growth hormone-secreting pituitary adenoma. More recently, it was shown that acromegaly may develop as a result of the secretion of GHRH by extra-pituitary tumors, resulting in pituitary somatotropic hyperplasia and GH hypersecretion. GHRH may be produced by the pancreatic islet cell tumors that commonly exist in MEN I patients. These pancreatic tumors may produce the hormones insulin, gastrin, somatostatin, glucagon and pancreatic polypeptide, and may, therefore, cause a variety of clinical symptoms.

Of the 11 proven pancreatic GHRH-producing adenomas reported in the literature, nine occurred in female patients. The mean age of these 11 patients was 39.8 years (ranging 21–58) and in only four of them was MEN I syndrome present beyond doubt. Our present report provides data on a family with MEN I syndrome, one member of which had a GHRH-producing adenoma, one has a clinically non-functioning adenoma and one has a prolactinoma.

Other sites of extrapituitary GHRH secretion are hypothalamic gangliocytomases, carcinoid tumors of the bronchus and foregut and the adrenal gland.

Although the prevalence of GHRH-secreting tumors in patients with acromegaly is less than 1%, the different therapeutic approaches to acromegaly due to different causes warrants efforts to establish the diagnosis. Surgery is the most effective treatment for acromegaly, but medical treatment with long acting somatostatin analogs, such as octreotide, has proved effective for many patients with classical acromegaly caused by a GH-secreting pituitary adenoma.

Patient A, who was treated surgically for his GHRH-producing tumor, was cured and remained in complete remission after a follow-up of over 10 years (which, to our knowledge, is the longest follow-up described in the literature for such a tumor). In our opinion, surgical resection, whenever feasible, taking into consideration the tumor location and patient’s condition, is the therapy of choice for extra-pituitary GHRH-producing tumors.

As most pancreatic islet tumors have a long doubling time, any patient with one should undergo lifelong follow-up. Such follow-up is also warranted for MEN I patients, because other organ involvement associated with MEN I syndrome may eventually become manifest. Analysis and follow-up is not only warranted for such patients themselves, but also in view of the genetic inheritance pattern, for their relatives, including present and future offspring.

References

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