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GASTRINOMA IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

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Abstract

Extensive experience from patients with gastrinoma as part of the multiple endocrine neoplasia type 1 (MEN 1) syndrome has revealed that MEN 1-gastrinoma patients show important differences from patients with sporadic gastrinoma. These differences comprise clinical, pathological and biochemical features, but are especially pertinent to the therapeutic approach. Therefore, the diagnosis of the MEN 1 syndrome is of great clinical importance to the gastrinoma patient and his family.

Key words: Gastrinoma, Zollinger-Ellison syndrome, multiple endocrine neoplasia type 1.

Gastrin-producing tumors occur as isolated lesions or as part of multiple endocrine neoplasia (MEN). The tumours are usually found in the MEN type 1 syndrome (Wermer's syndrome (1–4)), but have occasionally been described as a part of other forms of multiple endocrine disorders (5). Gastrin-producing tumours, nowadays called gastrinoma, may be asymptomatic, but usually give rise to clinical symptoms varying from 'ordinary' peptic ulcer disease to the full-blown Zollinger-Ellison syndrome, characterized by aggressive peptic ulcer disease, steatorrhoea and reflux oesophagitis (6). All these symptoms are due to gastric acid hypersecretion secondary to the acid stimulatory and trophic effects of gastrin on the parietal cells in the gastric body. The clinical symptoms of gastrinoma as part of the MEN 1 syndrome are not essentially different from isolated gastrinoma, although milder forms are often found due to family screening (7). Apart from gastrinoma, the MEN 1 syndrome may comprise hyperplasia or tumours in various endocrine organs, including the pituitary gland often secreting prolactin, parathyroid glands leading to hyperparathyroidism, the endocrine pancreas with hypersecretion of various polypeptides including insulin, glucagon, somatostatin, pancreatic polypeptide (PP), vasoactive intestinal polypeptide among various others, and nodular adrenocortical hyperplasia without established hormone hypersecretion (1–4). The tumours are often multicentric and may develop at almost any period during life-time, although the risk of developing new tumours is negligible before the age of 15 years and is low after age 50. The MEN 1 syndrome is inherited as an autosomal trait, but may occasionally be present without apparent familial involvement. The MEN 1 locus has recently been mapped to chromosome 11q 13 (8, 9). A central laboratory and register for endocrine tumours in Northern Ireland, with a population of about 1.5 million, has allowed an estimation of the frequency of gastrinoma occurring in the MEN 1 syndrome (10). Thirteen patients with gastrinoma, of whom 5 had the MEN 1 syndrome, were diagnosed from 1970 to 1985, giving an annual incidence of 0.05 for isolated and 0.02 for MEN 1 gastrinoma per 100 000 of the population. These data are in agreement with several other studies indicating that between 20 and 50% of gastrinoma occur in patients with the MEN 1 syndrome (2–4, 7, 11). In fact, gastrinoma is the most frequent pancreatic tumour in MEN 1, accounting for about 75% of the lesions (4, 11). The tumour usually develops between the ages of 20 and 40 years in patients who have previously manifested hyperparathyroidism (2–4, 11). Among the various other types of pancreatic tumours, insulinoma may also precede gastrinoma in the MEN 1 syndrome. Among more than 40 patients with MEN 1 gastrinoma studied in our institution, only one patient without previous parathyroidectomy was found to be normocalcaemic at the time of diagnosis of gastrinoma.

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This patient with hypoalbuminaemia and steatorrhoea became clearly hypercalcaemic during treatment with the potent gastric acid inhibitor omeprazole (12, 13).

Pathology

MEN 1 gastrinoma may arise from any part of the pancreas, but frequently occur, often as very small lesions, in the duodenal wall (14). They may metastasize to liver, lymph nodes and other organs. There are a number of differences betwen sporadic and MEN 1 gastrinoma. First, in sporadic gastrinoma the tumour is often solitary, whereas MEN 1 gastrinomas are usually multiple with new lesions developing in time. Second, MEN 1 gastrinomas are not found outside the pancreas or the duodenal wall, while sporadic gastrinoma may occur at ectopic locations, such as the ovaries, kidneys, liver, stomach and parathyroid glands (15). Third, MEN 1 gastrinomas are often associated with other types of endocrine tumours or endocrine cell hyperplasia of the pancreas. Mixed tumours do not seem to be more frequent in MEN 1 gastrinoma, and cosecretion of other polypeptides, e.g. ACTH, by a gastrinoma usually indicates rapid tumour growth accompanied by dedifferentiation (16). In fact, in the three MEN 1 gastrinoma patients with clinical symptoms of Cushing's syndrome seen in our institution, the hypercorticolism was due to an ACTH-producing pituitary tumour in two and an adrenocarcinoma in one, whereas none had ACTH production from pancreatic apudomas. Hypersecretion of clinically silent polypeptide hormones by the pancreas is rather frequent in MEN 1 gastrinoma (17, 18). We found that high plasma pancreatic polypeptide levels in gastrinoma usually points to the MEN 1 syndrome (17). Vipomas and glucagonomas also occur in patients with MEN 1 gastrinoma, but in our experience, at a rather low incidence.

Another interesting finding is that enterochromaffine cell like tumours (ECLomas) of the gastric body mucosa are almost exclusively restricted to MEN 1 gastrinomas (19). This indicates that apart from hypergastrinaemia a genetic predisposition appears to play a role in the development of these gastric tumours. A suggested high frequency of associated antral G-cell hyperplasia in MEN 1 gastrinoma (20) has not been confirmed by meal stimulation tests (21, 22).

Diagnosis

The diagnosis of gastrinoma is based on the demonstration of hypergastrinaemia and gastric acid hypersecretion. The finding that in MEN 1 patients elevated serum pepsinogen levels are restricted to those harbouring gastrinomas enables the diagnosis of gastrinoma in MEN 1 families by measuring gastrin and pepsinogen in a single blood sample (23). During family studies several MEN 1 gastrinoma patients without clinical symptoms have been diagnosed (11). We have further found that a positive secretin provocation test may precede the development of high basal gastrin levels and clinical symptoms by several years. As mentioned before, the presence of high plasma pancreatic polypeptide levels in a Zollinger-Ellison patient may also point to the MEN 1 syndrome (19). Interestingly, we have not encountered a single MEN 1 gastrinoma patient with a negative secretin provocation test, while we found a false negative test in about 20% of patients with sporadic gastrinoma (24). The only situation in which MEN 1 gastrinoma patients had a negative secretin test was when they were hypocalcaemic due to insufficient substitution therapy after parathyroidectomy (25). By stimulation using intravenous bombesin infusion or meal tests we could not confirm the suggestion that antral G-cell hyperplasia is part of the MEN 1 syndrome (21). Therefore, stimulation tests are not clinically indicated in patients with signs of gastric hypersecretion and unequivocal hypergastrinaemia.

Therapy

The multiplicity and multicentricity of pancreatic tumours in the MEN 1 syndrome precludes surgical cure of MEN 1 gastrinoma patients by tumour resection (26, 27). Total pancreatectomy and duodenectomy is the only procedures that may result in permanent cure. Because of the high morbidity of the resulting diabetes mellitus, this procedure is not justified in the majority of patients. Some authors feel that such a radical procedure may be indicated in those patients who have a very malignant course of the pancreatic tumours in their family (28). Therefore, treatment of MEN 1 gastrinoma can usually only be symptomatic. Since until recently complications of gastric acid hypersecretion, such as ulcer bleeding or perforation, were the main cause of death of MEN 1 gastrinoma patients, the importance of careful control of gastric hypersecretion should be emphasized. The H^+/K^+-ATPase inhibitor omeprazole with its potent and longacting antisecretory effect is the therapy of choice in these patients (13, 14). This drug will enable control of gastric hypersecretion in almost all patients with MEN 1 gastrinoma. However, since omeprazole is an acid labile drug, addition of antacids or intravenous omeprazole may be needed at the start of treatment. Furthermore, gastric acid secretion should be measured regularly, enabling tailoring of the dose of omeprazole. When doses higher than about 60 mg daily are needed, two daily doses instead of a single dose are preferable. Since omeprazole is available in almost every country, there is no place nowadays for the previously recommended forms of gastric surgery, such as vagotomy and total gastrectomy (29). Although parathyroidectomy is known to reduce serum gastrin levels and gastric acid hypersecretion in MEN 1 gastrinoma (30), gastric symptoms are no longer an indication for this procedure now that omeprazole is available. Several authors recommend resection of tumours in MEN 1

gastrinoma patients without documented liver metastases (27, 31). Since these tumours are often too small to be demonstrated by pre- or peroperative ultrasonography, CT-scan, MRI or angiography, percutaneous transhepatic venous sampling is often needed for localization (32). Resection of tumours may lead to reduction of serum gastrin and apparent cure of gastrinoma in MEN 1 patients. However, this improvement is often partial or transient. Therefore, prospective, controlled studies are needed to determine whether this reduction of tumour mass will result in a longer survival of the MEN 1 gastrinoma patients.

In patients with liver metastases several therapies have been applied. These comprise partial liver resection, hepatic devascularization, liver irradiation and various forms of chemotherapy. The conventional forms of chemotherapy are usually ineffective (33). In our experience, the combination of streptozotocin and 5-fluorouracil also carries a low efficacy. The somatostatin analogue SMS 201-995 may rarely induce reduction of tumour size, but this effect is usually transient (34, 35). More promising is the treatment with α-interferon (34, 35). This drug usually results in reduction of serum gastrin levels and may induce partial and even complete remissions. However, further studies are needed to determine the long-term efficacy of this treatment.

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