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SURGICAL TREATMENT OF ENDOCRINE PANCREATIC LESIONS IN MEN-1

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Abstract

The surgical treatment of endocrine pancreatic lesion in the multipel endocrine neoplasia syndrome type 1 (MEN-1) has remained a controversal issue. Histologic studies have revealed that the pancreatic lesions generally consist of numerous microadenomas, spread throughout the pancreas, together with occasional larger tumors. The patients may also harbor multiple, mainly gastrin secreting, duodenal microadenomas. A total pancreatectomy/duodenectomy should theoretically be needed for cure, but has not been recommended due to the associated mortality and morbidity, considering also the favorable prognosis of most MEN-1 patients. When pancreatic involvement in MEN-1 is biochemically diagnosed efforts should be made to localize the lesions by computed tomography, angiography and, in some patients, also transhepatic portal vein catheterization and venous sampling (PTP). Hypergastrinemia and the Zollinger-Ellison syndrome (ZES) generally constitute two-thirds of the clinically detected pancreatic lesions in MEN-1. Surgery may be undertaken in ZES-MEN-1 patients with focal lesions visualized by radiology or PTP in order to minimize the risk of malignant development in a gross tumor. Patients with insulin excess and hypoglucemia as well as the rare vipoma patient may, even in the absence of radiologically visualized tumors, be subjected to exploration, and these patients are usually found to harbor one or several gross tumors. The more frequent clinically silent, mainly PP-producing tumors should be removed when visualized by radiology. However, indications for surgery also have to emphasize an unusually malignant behavior in certain kindreds and patients may thus have to be explored when only biochemical data indicate the presence of pancreatic lesions. Pancreatic operations in MEN-1 should generally include a corpus and tail resection, together with enucleation of lesions in the pancreatic head, and in addition to that a careful duodenal exploration. Intraoperative ultrasound examination appears to be of considerable value by its ability to reveal also smaller lesions which may escape palpation.

Key words: Endocrine pancreatic tumor, multiple endocrine neoplasia syndrome type 1, surgery.

Prevalence

Endocrine pancreatic lesions may be demonstrated at autopsy in as many as 82% of patients affected by the multiple endocrine neoplasia syndrome type 1 (MEN-1; (1)). The clinical prevalence has generally been considerably lower (2), especially when screening detected cases have been included, and the pancreatic involvement has often been considered a late manifestation of the MEN-1 trait. More sensitive screening methods (3, 4) have, however, revealed probable endocrine pancreatic lesions in 75% of affected MEN-1 family members, and already during adolescense in some individuals (4, 5).

Histology

Histological investigations (6) have indicated that the MEN-1 pancreas should be invariably involved by diffuse nodular islet cell hyperplasia, nesidioblastosis (indicating proliferating endocrine cells arising from exocrine ducts) together with microadenomas (lesions measuring less than 0.5 cm in diameter), macroadenomas or islet cell carcinomas. The presence of the diffuse islet cell pathology has been questioned, however, mainly in view of the wide variation of the islet cell distribution in normal individuals and the difficulty to determine criteria for the hyperplasia diagnosis (7, 8). It has instead been suggested that

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microadenomas, being probably the most common lesion of the MEN-1 pancreas, may easily be misintrepreted as hyperplastic islets (7) and furthermore that nesidioblastosis may only variably be present (7). Most operated patients have had numerous microadenomas spread throughout the pancreas, and also gross tumors, of variable size, generally less than 2 cm, but occasionally up to 10 cm in diameter or more (6). The gross tumors have frequently been multiple, but never as numerous as the microscopic lesions, indicating special growth potential in large tumors.

Results of immunohistochemical studies have varied in different patient material (6, 7). Multiple hormones have been identified in 40–70% of detected tumors (6, 7). Klöppel et al. (7) found a high prevalence of pancreatic polypeptide (PP)-immunoreactive lesions, corroborating the value of basal or stimulated PP-measurements for screening in MEN-1 (3, 4, 9). Although larger tumors have frequently shown PP-immunoreactivity, no specific symptoms have been related to this hormone excess (10, 11). A predominant staining for glucagon was common in microadenomas (7), but not in the large tumors, and consequently MEN-1 patients may often have elevated serum-glucagon values, but seldomly a glucagonoma syndrome (5, 7). Insulinomas were almost as frequent as the PP-omas and glucagonomas, but only found in some patients. Neurotensinomas, somatostatinomas and vipomas were more rare (7). However, gastrinomas were in the series of Klöppel et al., as well as in other studies, surprisingly infrequent in pancreatic specimens (6, 7, 12). It is thus generally only occasional large tumors, that have displayed gastrin immunoreactivity, and the hormone has not been detected in the diffuse islet cell lesions (6). Corroborating the association of gastrin immunoreactivity mainly to the large lesions, it has been suggested that 'ectopic' gastrin production from pancreatic endocrine tumors may evolve with time in MEN-1 (5). A recent study by Pipelleers-Marichal et al. (13) further emphasized the infrequency of histologically verified gastrinomas located within the pancreas of MEN-1 patients with a Zollinger-Ellison syndrome (ZES). These authors studied eight patients with MEN-1 and hypergastrinemia and could in all cases demonstrate the presence of duodenal gastrinomas (13). The duodenal gastrinomas were characteristically small lesions, measuring around 2–3 mm or less, sometimes barely exceeding the size of a normal duodenal mucosal fold (13). The adenomas were as a rule multiple, up to 10 in one patient, and most of them stained postively for gastrin, but also for other hormones, somatostatin, sertonin and PP (13).

Incidence of malignancy

The incidence of proven malignancy in the MEN-1 pancreatic lesions has, with the exception of insulinomas, generally been lower than in the corresponding sporadic tumors. Thus, Thompson et al. (6) reported that 29% of MEN-1 patients harbored malignant tumors and a reported malignancy rate of 20% in the ZES-MEN-1 patients contrasted against the presence of metastastic tumor in about 60% of sporadic ZES-patients (14, 15). It was suggested, however, that MEN-1 patients may present early and other studies have in fact shown an equally high incidence of malignancy in MEN-1 as in sporadic ZES patients (16, 17). Although large tumors should more frequently be malignant, lymph node metastases have been found also in association with microadenomas (6, 7). However, long survival has been reported in MEN-1 patients both with large tumors and verified lymph node metastases, suggesting that the disease may frequently follow an indolent course (6). Thus, a 10-year survival of 70% was reported for MEN-1 patients with ZES contrasting against a 30% survival among those with sporadic disease (18). However, some MEN-1 families may apparently have pancreatic lesions with a more malignant behavior and poorer survival (5).

Moreover, Friesen (14) reported long-term follow-up in MEN-1 patients and found a considerable proportion of deaths occurring as a result of the progressive pancreatic tumor. Similar experience has been made in other material, and the pancreatic malignancy certainly is a principal cause of death in MEN-1 (19).

Pancreatic surgery in MEN-1

The surgical management of the pancreatic involvement in MEN-1 has been controversial, due to the multiplicity and the heterogeneity of the lesions, together with the often favorable, but variable, survival data. Theoretically a total pancreatectomy/duodenectomy should be needed to cure the patients, but the morbidity and mortality of this procedure have been considered unacceptable, because of the relatively benign course of the disease in most patients. Although there are variable opinions about selection of patients for surgery and what procedures to perform, surgeons dealing with MEN-1 patients operatively, invariably suggest that the strategy should put special emphasis on the clinical syndromes of hormone excess and also on the results of radiological tumor localization (16, 17, 20–24).

Operative strategy in relation to clinical syndromes

Pancreatic surgery in MEN-1 has generally been indicated for any of the syndromes of hormone excess, but the indications should also consider the threatening malignancy of various lesions (6).

The ZES syndrome is the most common clinical manifestation of the pancreatic involvement in MEN-1, being present in about two-thirds of the patients. Unfortunately, ZES-MEN-1 patients have in general been found virtually impossible to cure by operation, whether it be total pancreatectomy, pancreatico-duodenectomy or less radical

procedures. The introduction of medication providing efficient control of the gastric secretion, like H_2-receptor blockers or omeprazole, have almost completely abolished the need for operations directed towards the target organ, such as total gastrectomy or vagotomy. As a consequence, most authors have adopted a reluctant attitude towards surgery in the ZES-MEN-1 patients (18, 21, 22). Others advocate pancreatic surgery in ZES-MEN-1 patients with radiologically visualized tumors or in those with a localized hormone gradient demonstrated by percutaneous transhepatic portal vein catherization and venous sampling (PTP) (6, 17, 23, 24). Although this strategy may be unable to provide biochemical or clinical cure in most patients the removal of large tumors has been suggested to reduce the risk of malignant development (24). It is suggested that tumors of the pancreatic head should be removed by enucleation and that all cases should be subjected to a concomitant resection (75–85%) of the pancreatic corpus and tail (7), and also to a careful exploration of the duodenum in search for mucosal gastrinomas (7, 13).

About one-third of MEN-1 patients have insulinomas and associated hypoglucemia syndrome (20). The MEN-1 insulinomas have been claimed to constitute 4% of all insulinomas, but the proportion may be slightly higher (20). Insulin immunoreactivity is frequently demonstrated in pancreatic microadenomas in MEN-1 while the hypoglucemia syndrome is generally restricted to patients with one or several larger lesions (7, 20). The MEN-1 insulinomas often present in the second or third decades of life, which is significantly earlier than in most patients with sporadic insulinomas (20). Like other MEN-1 lesions, they have not been encountered in infancy, but occasionally in the elderly (6). Medical management with diazoxide has appeared difficult to apply in this population (24). The hypoglucemia syndrome of MEN-1 patients can apparently often be cured by surgery and alleviance of hypoglucemia as well as the excess insulin secretion has generally been reported after excision of solitary or, more often, multiple insulinomas (20). As the source of the insulin excess frequently is multifocal it is considered important to combine enucleations of caput insulinoma with distal resection of the pancreas (20). The recommended 75–85% corpus and tail resection should not cause diabetes, except in occasional patients with a family history of this disease (20). A high persistence and recurrence rate, approximately 40%, may be encountered among operated MEN-1 insulinomas, necessitating repeated tumor enucleation, which is generally recommended, even at the risk of causing permanent exocrine and endocrine insufficiency (20).

In the more rare patients with MEN-1 and the vipoma syndrome surgical exploration is indicated, as in patients with hypoglucemia, irrespectively of if a tumor is preoperatively visualized or not (24). It is preoperatively often important to obtain control of the severe diarrhea and electrolyte disturbances by medical management, usually with the somatostatin analogue, Sandostatin, which often is effective. In patients with metastases, repeated debulking surgery may be considered due to the severity of associated symptoms.

Frequently MEN-1 patients appear with clinically silent tumors, many of them secreting an excess of PP, somatostatin or various combinations of hormones, not related to specific clinical symptoms. Also these tumors should be removed according to principles outlined for clinically overt tumors.

Radiological visualization of pancreatic tumors

One of the obstacles in the surgical treatment of MEN-1 patients has been the difficulties to localize pancreatic lesions by radiological methods (25). Our own recent study (Skogseid et al. Unpublished data) of localization methods in MEN-1 patients thus revealed, as has been reported for sporadic endocrine pancreatic tumors (26), a poor sensitivity of percutaneous ultrasound. CT and angiography were both more sensitive, but also missed some of the larger lesions, and virtually all of the generally multiple microadenomas (Skogseid et al. Unpublished data). Similar results have been reported by Shepard et al. (24), indicating that CT and angiography could identify 80% of large tumors in MEN-1, but not smaller lesions. Either of these methods, preferably CT, may also establish the presence of hepatic metastases in patients with MEN-1. PTP is considered to have probably the highest sensitivity for sporadic as well as for MEN-1 associated endocrine pancreatic tumors (24, 26). The method is invasive, however, and not suitable for repeated investigations and, apparently also associated with false positive results, although this may be questionable as areas with hormone gradients have not always been surgically resected ((26) and Skogseid et al.: Unpublished data). The method may be of value in MEN-1 patients by determining the association between various tumors and excess secretion of a specific hormone. Thompson et al. (6, 23) reported that localization by PTP allowed resection of gastrinomas from areas of excess gastrin secretion and a resulting occasional cure of patients with ZES-MEN-1. However, others adopting the same strategy have been unable to cure any of their patients (24). The intraarterial secretin stimulation test may perhaps provide a more efficient preoperative localization of gastrinomas also in MEN-1 patients, as recently demonstrated in sporadic ZES patients (27).

Several authors have emphasized the value of intraoperative ultrasound for imaging of endocrine pancreatic tumors (28–31). The method is advantageous, also by establishing relations between the endocrine pancreatic tumors and the choledochus as well as the pancreatic duct. In our recent study of localization methods in MEN-1 patients (Skogseid et al. Unpublished data) palpation following a careful exploration revealed several pancreatic

tumors measuring 0.5–1.5 cm diameter, which had escaped detection by preoperative imaging. Palpation generally revealed tumors larger than 0.5 cm, while the intraoperative ultrasound could image most lesions larger than 0.3 cm. The intraoperative ultrasound also provided a more reliable localization of larger tumors. Moreover, it was of value by determining pancreatic resection lines necessary for inclusion also of barely palpable tumors.

During recent years we have surgically treated 18 individuals with various MEN-1-related pancreatic lesions. We have adopted the policy to explore patients with hypergastrinemia, without hepatic metastases but with radiologically visualized lesions or focal sources of gastrin excess, suggested by PTP and venous sampling. Patients with insulinomas and vipomas have been explored irrespectively of radiological findings, but PTP and venous sampling have been utilized to determine specific sites of hormone production. Patients with non-functioning tumors are also subjected to surgery when lesions are imaged by radiology.

The patients have belonged to several unrelated kindreds, and many of them have been detected during screening studies within the different families (5). The internal physicians screening these kindreds have noted considerable variations between families in expression of the pancreatic disease, both with respect to peptide excess and malignant behavior (5). Certain kindreds with a general malignant behavior of endocrine pancreatic lesions will therefore be submitted liberally to surgery, on basis merely of biochemical evidence for pancreatic involvement (5). On the other hand, patients belonging to families with a benign disease course will, if they have a ZES syndrome, rather receive medical therapy. An increased efficacy of screening for pancreatic lesion in MEN-1 may increase the demands for early surgery in these patients, mainly in the hope of removing lesions before they have metastazised. However, it may be problematic to perform extensive pancreatic surgery in young individuals and it should then be more crucial to select therapy with respect to the malignant behavior within a specific kindred (5). Moreover, before really early surgery in MEN-1 patients is undertaken, further studies are probably needed to clarify pancreatic and duodenal histopathology as well as malignant potential within specific lesions and long-term follow-up in various kindreds.

Operative exploration of the MEN-1 pancreas

At laparotomy the head of the pancreas, including the uncinate process is mobilized by an extended Kocher's maneuver. After division of the gastrocolic ligament, the pancreatic body and tail are dissected free from the underlying retroperitoneal tissue, and the neck of the pancreas is partially separated from the superior mesenteric vessels. Following this procedure a careful bidigital palpation of the whole pancreas is performed and the entire gland is scanned repeatedly with intraoperative ultrasound, both from the anterior and posterior surfaces. Even the larger lesions located in the head of the pancreas generally lend themselves to enucleation and this is in virtually all patients combined with a 75–85% distal pancreatic resection, removing the entire corpus and tail. A long duodenotomy is also performed in all patients and a careful search is instituted for the identification of minimal lesions. Clearance of lymph nodes around the pancreas and the duodenum is also performed in all cases. Repeated tumor enucleation or pancreatic resection may have to be performed. Moreover, larger or malignant lesions, especially when associated with a severe clinical syndrome, may have to be removed by a pancreaticoduodenoectomy. Repeated operation for recurrent tumor may also result in a near total or perhaps total pancretectomy but neither of these procedures has as yet been performed in our MEN-1 patients.

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