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Localisation and surgical treatment of insulinomas*

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SUMMARY

Most insulinomas are solitary, benign and functional neuroendocrine pancreatic tumours which give rise to manifold symptoms. Their preoperative localisation is often unclear, but the cure rate after their excision is very high. It was the aim of this study to analyse and evaluate our group of patients with regard to preoperative tumour localisation and overall surgical results. Twelve patients with a biochemical diagnosis of organic hyperinsulinism were surgically treated. Diagnosis was made with the combination of magnetic resonance imaging, computed tomography, selective angiography and intraoperative portal vein sampling. In five patients, the tumour was enucleated, in three patients Whipple procedure was performed; while three patients underwent left pancreatectomy with spleen preserving in two cases. The twelfth patient underwent total pancreatectomy following Whipple procedure performed elsewhere. There was no postoperative death. The complications were two pancreatic fistulas and two wound infections. The fasting pre- and postoperative plasma glucose mean value was 2.8 mm/l and 4.9 mm/l, respectively; while the pre- and postoperative plasma insulin mean value was 282 pm/l and 72 pm/l, respectively. Accurate diagnosis, preoperative localisation and diligent surgical exploration by experienced surgeons are the key to a successful outcome in patients with insulinomas.

Introduction

Pancreatic endocrine tumours are rare lesions, with a reported incidence of four cases per one million patients per year (1). Of these lesions, insulinomas are the most common. It was first described by Wilder in 1927 (2), and it was in 1929 when Graham performed the first surgical exploration of an insulinoma (3).

The majority of patients diagnosed with an insulinoma are between 30 and 60 years of age, with women accounting for 59% (4,5). Most insulinomas are sporadic in origin. In two series, 7.6 and 12% of patients with insulinoma had multiple endocrine neoplasia type I (MEN I) syndrome (1,6). Insulinomas are more likely to be multiple in patients with MEN I (1,6).

Patients with insulinoma have symptoms of hypoglycaemia resulting from neuroglycopenia and increased catecholamine release. Neuroglycopenic symptoms are most common, including anxiety, dizziness, lightheadedness, personality changes, unusual behaviour, confusion, incoherence, blurred vision, seizures and coma. Sympathoadrenal signs and symptoms, such as palpitations, tremulousness, diaphoresis and tachycardia, may also be present and are due to catecholamine release in response to low serum glucose levels (7).

Surgical excision is the treatment of choice and is curative in most cases. At the time of surgery, the majority of these lesions are found to be solitary, equally distributed throughout the pancreas and less than 2 cm in diameter. Huai et al. report that preoperative-imaging studies and surgical exploration fail to localise the tumour in 20 to 60% and 10 to 20% of the patients', respectively (8). When tumours are not localised, blind resection may be required with a rate of complications as high as 31.5 to 55% (8).

In this report, our experience of the diagnosis, localisation and surgical management of insulinoma are reviewed.

Methods

From 1 January, 1998, to 31 December, 2004, 12 patients (four male and eight female) with a biochemical diagnosis of organic hyperinsulinism were referred for assessment and surgical treatment. The age of our patients ranged from 34 to 65 years, with a mean age of 47 years.

The most common presenting symptoms were related to severe neuroglycopenia (12 patients, 100%). Hypoglycaemic seizures and confirmed weight gain were presented in four (36%) and eight (73%) patients, respectively. The duration of symptoms before diagnosis ranged from 18 to 32 months, with a mean duration of 25 months.

The diagnosis was confirmed by documenting fasting hypoglycaemia and by measurement of serum glucose, insulin and C-peptide levels and by measurement of HbA_1C. The diagnosis of insulinoma was established by Whipple's triad (9) and inappropriate elevation of serum insulin. All the diagnostic parameters in patients with insulinoma before and after the surgical treatment are summarised in Table 1.

After biochemical confirmation of the diagnosis, preoperative localisation of the tumour was attempted. Preoperative studies were done in all the patients. All patients underwent a combination of abdominal computed tomographic (CT) scan, magnetic resonance imaging (MRI) and selective angiography. Intraoperative portal vein sampling (IPVS) was performed in two patients. In one patient (8.3%), the preoperative studies failed to localise the tumour. The tumour that was not detected was 1 cm in diameter. The 1-cm tumour was situated in the tail of the pancreas.

A total of 12 operations were performed; 11 were primary and one was reoperation (second reoperation). All operations were performed in a similar manner. A standard supraumbilical transverse incision was made transecting both recti muscles. The head of the pancreas was exposed by performing an extended Kocher maneuver, and the body and the tail were exposed by entering the lesser sac and dividing along the inferior border of the pancreas. The whole pancreatic gland was then manually palpated. Occasionally, the spleen was mobilised to facilitate visualisation and palpation. In two cases, IPVS was performed to localise a specific region with the insulinoma. If a tumour was detected, and the location corresponded to that found on preoperative localisation studies or the IPVS, the tumour was resected by enucleation when deemed feasible or formal pancreatic resection. No blind resections of the pancreas were performed.

Table 1 Diagnostic parameters in patients with insulinoma pre and postoperatively

	Before procedure	After procedure (3–8 months)
Age (years)	74 ± 3	74 ± 3
Gender	4M/8F	4M/8F
Weight (kgr)	81 ± 6	76 ± 5
BMI (kgr/M^2)	37 ± 3	29 ± 3
HbA1C (%)	4.0 ± 0.1	5.6 ± 0.2
Fasting plasma glucose (mM)	2.8 ± 0.2	4.9 ± 0.2
Fasting plasma insulin (pM)	282 ± 52	72 ± 10

Results

Enucleation of the tumour was performed in five cases, Whipple procedure was performed in three patients; while three patients underwent left pancreatectomy with spleen preserving in two cases. The 12th patient underwent total pancreatectomy following Whipple procedure which was performed elsewhere.

The final histopathological diagnosis was solitary islet cell adenoma in nine patients, multiple islet cell adenomas in two patients (including the patient who underwent re-exploration), and neuroendocrine carcinoma in one patient. Three of these tumours were located in the head of the pancreas (25%), two were in the neck (16.7%), one was in the body (8.3%), five in the tail (41.6%), and in one patient. there were multiple tumours (8.3%). These tumours ranged from 0.5 to 3 cm in size.

The tumour detection rates of abdominal CT, selective angiography, MRI imaging and intraoperative IPVS among our patients and the sensitivities of tumour localisation were 58.3% (seven of 12 cases), 83.33% (10 of 12 cases), 71.43% (five of seven cases) and 100% (two of two cases), respectively.

There was no postoperative death. Complications occurred in four of the 12 (33.3%) patients: two pancreatic fistulas, which were treated conservatively and two wound infections. No patient was reoperated. Diabetes mellitus developed in one patient after a total pancreatectomy.

The median postoperative follow-up was 16 months (ranged from 6 to 24 months). No recurrent hypoglycaemia occurred (Table 1).

The case of two brothers who both had insulinoma should be noted. The first one, who had been surgically treated elsewhere twice (Whipple procedure and enucleation), was reoperated, and a total pancreatectomy was performed due to additional insulinoma in the tail of the pancreas. The other one underwent enucleation of two insulinomas. The histopathological diagnosis showed neuroendocrine carcinoma of the pancreas. He is in a good condition 2 years postoperatively.

Discussion

Insulinoma, with an incidence of 1/1000000, is the most common functioning islet cell tumour. It arises

from islet cells and produces insulin, leading to symptoms of hypoglycaemia. Treatment of insulinoma requires surgical management. Enucleation or left pancreatectomies for these tumours are performed. Most insulinomas are solitary, benign, devoid of metastasis, less than 1.5 cm in diameter and located in the anterior aspect of the body and tail of the pancreas.

In 1935, Whipple and Franz (9) described a triad of clinical findings that were unique to patients with insulinoma: symptoms of hypoglycaemia, a plasma glucose level of 45 mg/dl (2.5 mmol/l) or less when symptoms of hypoglycaemia occurred, and relief of symptoms with the administration of glucose. More recently, Service (10) recommended the following biochemical criteria to establish a diagnosis of insulinoma in the absence of renal insufficiency: an insulin level of 36 pmol/l or more as measured by radioimmunoassay (RIA) or of 18 pmol/l or more as measured by an immunochemiluminescence assay, a C-peptide level of 200 pmol/l or more, and a proinsulin level of 5 pmol/l or more in a patient with a serum glucose level of 45 mg/dl (2.5 mmol/l) or less, a negative plasma sulphonylurea screen (including repaglinide) and negative insulin antibodies. Vezzosi et al. (11), using a modern insulin-specific immunoradiometric assay, have documented insulin levels below 18 pmol/l in patients with symptomatic hypoglycaemia of 45 mg/dl or less from small insulinomas. They concluded that insulin levels are dependent on the assay employed and its cross-reactivity with proinsulin, and they emphasised that concomitant measurement of C-peptide levels is mandatory for establishing a diagnosis of insulinoma (11). In most patients with insulinoma, a diagnosis is established by a supervised fast during which simultaneous measurements of glucose, insulin and C-peptide are obtained. On this study, the patients had a serum preoperative glucose level of 2.8 ± 0.2 mm/l and typical symptoms of hypoglycaemia that were relieved by i.v. glucose; while the preoperative plasma insulin mean value was 282 pm/l.

Ultrasound (US), CT, angiography and transhepatic portal venous sampling (THPVS) have been widely used in the preoperative localisation of the tumours with various accurate localisation rates reported by many investigators (12). The results of non-invasive-imaging techniques, in general, have been discouraging. Sensitivities ranging from 9 to 63% and from 16 to 72% have been reported for US and CT scanning, respectively (13). Higher sensitivity (ranging from 36 to 91%) has been reported for angiography (13). The best results were obtained by THPVS along the pancreatic vein: a sensitivity of 82% and a specificity of 91% were reported by Vinik (14). The multicentre studies collected by Proye and Boissel (15) showed the successful rate of preoperative localisation was 70.3%.

Some centres use preoperative endoscopic ultrasound, which has reported accuracy rates of 60–90% (16). Lesions in the tail may be missed using endoscopic ultrasound; however, these lesions are usually easily identified intraoperatively (17). Approximately, 40% of all insulinomas are not localised preoperatively, and between 3 and 10% remain occult even after intraoperative palpation and the use of intraoperative ultrasound (5,6).

In this study, the combination of preoperative abdominal CT, MRI and selective angiography successfully localised the tumours in 10 of 12 cases (83.33%). Portal venous sampling was not necessary to be used preoperatively, even in the only case of occult insulinoma. This invasive technique, although helpful, cannot give the precise anatomical localisation and indicates only the region of the pancreas from which the excess insulin secretion emanates (18).

We performed IPVS in two cases, and we found it to have a true positive rate as high as 100%. Our limited experience, similar to other authors (19), showed that IPVS is a simple, highly reliable tool for predicting the completeness of surgery in patients with organic hypoglycaemia.

Some authors consider endoscopic ultrasonography (EUS) to be the single most important preoperative localisation study needed (17,20). Localisation of an insulinoma with laparoscopic ultrasonography has also been reported (21–23). An impressive overall sensitivity of 95 to 100% by a combination of surgical exploration with palpation and use of intraoperative ultrasonography by experienced surgeons made the need of preoperative localisation doubtful. In this study, neither endoscopic nor intraoperative ultrasonography were used as not available, but we agree that a surgeon with appropriate training and experience may be able to palpate the tumour at operation with high accuracy. Intraoperative palpation and ultrasound are the gold standards for localising an insulinoma, with a reported success rate of 96–100%.

We also agree with those authors (18,24,25) who believe that accurate preoperative localisation helps direct operative strategy, minimising operative trauma and reducing unnecessary biopsy.

No blind resections were performed in our cases. Today, with so many localisation studies available, blind pancreatectomy is not a reasonable strategy for patients with occult insulinoma (26). Mengoli and Le Quesne (27) found that an insulinoma was removed in only 12 of 47 patients who underwent blind distal pancreatectomy.

Our mortality rate of 0% was excellent, and the complication rate of 33.3% is comparable with the 10 to 43% reported in different series (13,28).

In summary, after positive biochemical and fasting tests and exclusion of diffuse abdominal metastases, all patients should undergo surgical excision of the insulinoma.

The goal of treatment of a patient with an insulinoma is to identify and excise the primary tumour and, when possible, all metastatic disease.

Accurate diagnosis, preoperative localisation and diligent surgical exploration by experienced surgeons are the key to a successful outcome in patients with insulinomas.

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