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Pancreatic Insulinomas - A Study of 15 Cases From 1978 - 98

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Summary

Fifteen cases of insulinoma were managed at HUKM over a period of 20 years. Although all patients presented with neurological symptoms, the diagnosis was delayed in all. Fasting hypoglycaemia and the measurement of C-peptide levels eventually made the diagnosis. Pre-operative localization investigations were not particularly useful. Intraoperative ultrasound (IOUS) detected 72% of the insulinomas, while 93%of the insulinomas were identified intraoperatively by palpation. All the insulinomas were detected intraoperatively with the combination of the two techniques. Twelve of 15 patients had benign adenomas including one patient with MEN-1 syndrome. Two patients had malignant insulinomas. One patient refused surgery. Nine patients underwent pancreatic resections and the remaining 5 patients had the adenomas enucleated.

Key Words: Insulinoma, Diagnosis, Localization, Surgical treatment

Introduction

Insulinomas are the most common of the endocrine pancreatic tumours with an incidence ranging from 4 to 5 cases per million[1,2,3]. Insulinomas are commonly solitary and benign[2], with an equal distribution throughout the head, body and tail of the pancreas[3]. They are rarely ectopic but may be multiple when they occur as part of multiple endocrine neoplasia (MEN) type 1 syndrome[3]. Cure can be obtained by surgical excision. We present our experience of 15 cases over a period of 20 years.

Materials and Methods

Fifteen patients with pancreatic insulinomas were treated from mid 1979 to January 1999. There were 8 males and 7 females. The mean age of presentation was 43.2 years (range 22 - 66 years). The duration of symptoms ranged from 2 to 10 years prior to diagnosis. The presenting symptoms are as tabulated in Table I.

Laboratory tests consisted of measurement of fasting blood glucose and C-peptide levels. Pre-operative localization studies included use of ultrasonography, CT scan, angiography and, since 1997, Arterial Stimulation Venous Sampling of C-peptides (ASVS) to regionalise the tumour (Table II). Intraoperative palpation was performed in all cases and intraoperative ultrasound (IOUS) used since 1995 (Table II).

Results

There were 8 males and 7 females. Eight patients were Chinese and 7 were Malays. The mean age of these patients was 43 years (range 22 - 66 years). Multiple

Table I
Presenting Symptoms in Patients with Insulinoma

System	Symptoms	n
Neurological	Sleepiness	15
	Headaches	15
	Syncope	15
	Fits	6
	Altered behavior	4
Gastrointestinal	Hunger	5
	Nausea	5
	Weight gain	5
Cardiovascular	Sweating	2
	Palpitations	2

Table II
Results of Pre-operative and Operative Localization Techniques in Patients with Insulinomas

Investigation	n	Sensitivity (%)
Pre operative ultrasound	2	0
Preoperative angiogram	7	42
Preoperative CT Scan	13	38.5
Preoperative ASVS	3	33.3
Intraoperative palpation	14	92.8
Intraoperative ultrasound (IOUS)	7	71.5

endocrine neoplasia type 1 was diagnosed in a 33-year-old Chinese lady who was found to be hypercalcaemic after the treatment of insulinoma.

Presentation, investigations and localization

All patients presented with neurological symptoms and 2 patients had additional cardiovascular symptoms. Five patients had a gain in weight (Table I). The duration of symptoms ranged from 2 to 10 years before the diagnosis of insulinoma was made. The fasting blood sugar levels ranged from 1.2 to 2.2mmol/l (mean = 1.7mmol/L). In the early period before the availability of C-peptide levels, Whipples triad (signs and symptoms of hypoglycaemia during periods of fasting or exercise, documented hypoglycaemia at time of symptoms, and reversal of symptoms with administration of glucose) was used to diagnose the insulinomas (n=4). C-peptide levels were measured in 11 patients and raised in 91% (n=10) of the patients. The mean C-peptide level was 2.06 pmol/L, with a range of 0.125 - 6.23 pmol/L (normal = 0.11 - 0.39pmol/L). Only one patient had a normal C-peptide level. Preoperative localization studies included ultrasonography (n=2), CT scanning (n=13), angiography (n=7) and ASVS (n=3). The sensitivity of the preoperative localization techniques is shown in Table II. With all the preoperative localization techniques, only 8 of the 15 insulinomas were localized preoperatively.

Table III
Distribution of Pancreatic Insulinomas

Location	n
Head	5
Neck	1
Body	4
Tail	4

Intraoperative findings

Intraoperative palpation by an experienced surgeon was performed in all cases. Two tumours were obvious and the remaining 12 were palpable. The size of the tumours ranged from 0.5cm to 4cm in diameter. In one patient, a tumour measuring 0.6 x 0.6 x 1.2cm over the upper border of the head was missed during palpation but was detected by IOUS. IOUS became available in 1995 to our unit and subsequently we assessed the sensitivity of IOUS on all patients prior to performing intraoperative palpation. The IOUS was performed on 7 patients and the sensitivity was 71.5%. All the tumours were solitary. Of the 2 patients with malignant insulinomas, one had multiple liver metastases while the other had a tumour measuring 3 x 2 x 2cm at the inferior aspect of the head and uncinate process with local infiltration and multiple para-aortic lymph nodes. The insulinomas were equally distributed in the pancreas as follows, head (n=5), neck (n=1), body (n=4), and tail (n=4). One patient refused surgery.

The surgical procedure performed in each case was determined by the nature and position of the insulinoma. The surgical procedures performed on the

14 patients included enucleation (n=5), distal pancreatectomy (n=7), Whipple's procedure (n=2). Histopathology confirmed benign insulinomas in 12 patients (85.7%) and malignant insulinomas in two (14.3%). One patient who underwent Whipple's procedure died on the 5th post-operative day. Four patients developed transient hyperglycaemia. Thirteen patients became euglycaemic. One patient with a malignant insulinoma and liver metastases underwent chemoembolisation with lipoidol, gelfoam and Adriamycin. He was continued on diazoxide and succumbed to the disease 3 years following surgery. Another female patient was found to be hypercalcaemic with raised parathyroid hormone (PTH=106.9pmol/l) during follow-up. She was diagnosed to have MEN 1 syndrome. She underwent a right superior parathyroidectomy 6 months after the distal pancreatectomy. All the remaining patients including one with malignant insulinoma are well and euglycaemic.

Discussion

Insulinomas are the most common endocrine tumour of the pancreas. Howland and co-workers reported the first surgical cure of an insulinoma in 1929[4]. In our series, although all the patients presented with neurological symptoms the diagnosis was delayed for up to 10 years. The diagnosis in our first four cases was based on Whipple's triad. The ability to measure C-peptide levels has greatly improved the diagnosis of insulinomas. The diagnosis is based on fasting hypoglycaemia and inappropriately raised C-peptide levels[4]. C-peptide levels are useful in diagnosing insulinomas in patients with diabetes or in eliminating hyperinsulinism due to exogenous injections of insulin[5]. Stimulation tests presuppose the sensitivity of the tumour cells to stimuli. The tolbutamide stimulation test gives 80% accuracy while the glucagon stimulation test has a 72% accuracy[4]. Insulinomas respond to a rise in serum calcium concentrations by discharging the contents of their secretory granules and thus raising the levels of proinsulin, insulin and C-peptide. This forms the basis of the calcium infusion test[4-8]. Fasting blood sugar and measurement of C-peptide levels improved the accuracy of diagnosis from 90% to 100%.

Preoperative localization of the insulinomas was disappointing; ultrasonography was accurate in none of cases, CT Scan in 38.5%, angiography in 40%, ASVS in 33.4%. These figures are in keeping with published data[9]. The low accuracy of ASVS at our Institution may be due to the learning curve of the procedure. There is some evidence that dual phase spiral CT (DPSCT) can improve preoperative localization of insulinomas[10,11]. The sensitivity of intraoperative localization by palpation was 93% and 72% for IOUS, and these figures are again in keeping with published data[3,12].

The only curative treatment for insulinomas is surgical excision of the tumour, however as insulinomas are usually small (40% < 1cm diameter, 65% < 1.5cm and 90% < 2cm)[4,5], there may be difficulty in locating the exact site of the insulinoma preoperatively, thus emphasizing the importance of preoperative localization. A broad range of sensitivities has been reported in the literature regarding the success of various preoperative localization techniques[6]. Selective coeliac axis angiography had been considered the modality of choice for localizing these tumours at the Mayo Clinic with sensitivities of up to 95% being reported[7]. However, there is a decrease in its accuracy and use in more recent experience[8]. Sophisticated techniques of percutaneous transhepatic venous sampling or intra-arterial calcium stimulated venous sampling has been reported to achieve accuracy rate between 67% to 95%[3,5,6]. This test is invasive, expensive, time-consuming and not available in most surgical centres. These tests do not accurately localize the insulinoma but tend to regionalize the tumour to a specific area of the pancreas[6]. Menegaux et al reported 22% morbidity in selective coeliac and superior mesenteric angiography and after transhepatic catherization[5]. Intraoperative ultrasonography when combined with manual palpation of the pancreas results in insulinoma localization in 95% to 100% of patients. IOUS can delineate the proximity of the main pancreatic duct to the tumour. This information can aid the surgeon in choosing between enucleation or pancreatic resection[2,5,6,12]. The current surgical trend for a single tumour regardless of site is to perform enucleation. Pancreatic resection is indicated if the tumour is situated deep within the gland, close to the pancreatic duct or when there are multiple tumours or hyperplasia

of islets of Langerhans[5]. The surgical treatment for our patients was based on this view, and consisted of enucleation in 35.7%, distal pancreatectomy in 50% and Whipple's procedure in 14.3%. Current literature review recommends a subtotal pancreatectomy with enucleation of tumours from the pancreatic head and uncinate process in patients with MEN 1[13,14].

Eighty-six percent (86%) of our patients had benign insulinomas. There was one post-operative mortality (7%) following a Whipple's procedure but there was no morbidity apart from transient hyperglycaemia in 4 patients (28.6%). One patient with malignant insulinoma is still on follow-up after 6 years but the other with liver metastasis succumbed to the disease after 3 years. One patient had MEN 1 syndrome in our series.

Insulinomas continue to be a challenge from both a diagnostic and therapeutic viewpoint, and a high degree of clinical awareness is needed in patients with symptoms suggestive of hypoglycaemia. Preoperative localization studies render disappointing results. Intraoperative manual palpation with IOUS will localize the insulinoma with greater accuracy. IOUS will also help the surgeon to decide between enucleation and pancreatectomy. As insulinomas are rare and the outcome of surgery depends on the availability of an intraoperative ultrasound and an experienced surgeon, these patients should be referred to the appropriate referral centre following diagnosis[15].

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