PROBLEMS IN THE MANAGEMENT OF INSULINOMA

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SYNOPSIS

Insulinoma is a rare tumour. The diagnosis and management present many problems. Two cases of insulinoma are reported and the problems in the diagnosis and management are discussed.

INTRODUCTION

The diagnosis of insulinoma should be considered in any patient who presents with bizarre behaviour or disturbance of consciousness in a fasting state. The demonstration that these symptoms are due to hypoglycemia and are relieved by the administration of glucose constitute the well known Whipple's triad. Definitive diagnosis requires the demonstration of inappropriately high endogenous plasma insulin levels in the presence of hypoglycemia and the localisation of the tumour. Once diagnosed, the treatment is primarily surgical except in the very ill. Postoperatively other medical problems such as hypoglycemia may be encountered.

In this paper we report 2 cases of insulinoma, and illustrate the problems in their diagnosis and management.

CASE 1

KKC, a 37 year old female clerk presented with many episodes of generalised seizures over a 2-year period. These attacks occured in the morning when she had a late breakfast or no breakfast at all. She tried not to miss any meals because she would invariably develop giddiness, drowsiness and tremors.

On examination, no physical abnormalities were detected. No neurological deficit was found except for some slowness of her mentation. The fasting blood glucose was 40mg%

Prolonged fasting was carried out. Simultaneous plasma glucose and insulin assays were done. The results are in Table 1.

TABLE 1:
CASE 1: RESULTS OF SIMULTANEOUS ASSAYS OF PLASMA AND INSULIN LEVELS AFTER PROLONGED FASTING.
(NORMAL RANGE OF PLASMA INSULIN LEVEL 1-13mU/L)

Hours of Fast	12½	15	19½
Plasma Glucose in mg%	30	30	28
Plasma Insulin in mU/L	13.6	23.6	11.5
Insulin/Glucose ratio	0.453	0.787	0.442

In view of the abnormal plasma insulin/glucose ratio, the diagnosis of insulinoma was made.

To localise the tumor, an ultrasound examination, CT scan of the abdomen, coeliac axis angiogram and a percutaneous transhepatic portal venography and sampling (PTPVS) of plasma insulin, glucose and C-peptide were done. Both the insulin and C-peptide were measured by radio-immunoassay.

The ultrasound, CT scan and coeliac axis angiogram all reported a tumor in the head of the pancreas. The PTPVS localised the tumor in the tail of the pancreas.

The PTPVS results are shown in Fig 1 and Table 2.

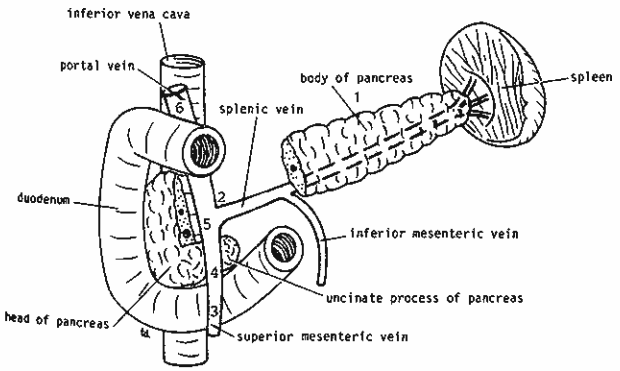

TABLE 2:
CASE 1: RESULTS OF PERCUTANEOUS TRANSHEPATIC PORTAL VENOUS SAMPLING OF PLASMA GLUCOSE, INSULIN AND C-PEPTIDE LEVELS.
THE SITES NUMBERED 1 TO 6 CORRESPOND TO THOSE IN FIGURE 1.
(NORMAL RANGE OF SERUM C — PEPTIDE: (0 — 5.4 ng/ml)

Site	Plasma Glucose in mg%	Plasma Insulin in mU/L	Insulin/ Glucose Ratio	Serum C-Peptide in mG/ml
1	43	283.6	6.60	2.9
2	43	94.4	2.20	1.6
3	38	14.5	0.38	0.5
4	41	92.9	2.27	1.7
5	35	39.0	1.11	1.0
6	35	56.4	1.61	1.0

At surgery, several small nodules of 1 cm diameter were detected in the body and tail of the pancreas. Frozen section of these nodules confirmed the diagnosis of beta-cell adenomata. A distal pancreatectomy was done.

Throughout surgery, the patient was on a normal saline drip. Intraoperative blood glucose monitoring was done and the results are shown in Table 3.

Postoperative recovery was uneventful. A simultaneous sampling of the fasting plasma glucose and insulin was repeated on the 7th and 30th postoperative day and were found to be normal.

TABLE 3:
CASE 1: RESULTS OF INTRAOPERATIVE MONITORING OF PLASMA GLUCOSE. THE LEVELS OF THE PLASMA INSULIN, INSULIN/GLUCOSE RATIO, AND C-PEPTIDE ARE ALSO SHOWN.

Event	Time in A.M.	Plasma Glucose in mg%	Plasma Insulin in mU/L	Insulin/ Glucose ratio	Serum C-Peptide in ng/ml
Start of	8.30	48	23.7	0.494	0.5
Surgery	9.00	31	37.2	1.200	1.6
	9.50	53	19.5	0.380	1.5
Distal	11.00	65	11.1	0.170	0.2
Pancrea-					
tomy	11.05	74	13.4	0.180	0.0
Comple-	11.30	96	9.8	0.100	0.3
ted	11.45	98	9.8	0.100	0.3

CASE 2

STW, a 52 year old housewife was investigated for excessive drowsiness and abnormal behaviour for 6 months. The family often found her difficult to arouse in the morning. She was also noted to talk incoherently and had strange behaviour before breakfast. These episodes were associated with perspiration. One morning she was found unarousable. A private practi-

tioner saw her and took a sample of blood for glucose estimation: it read 34mg%. The patient was given intravenous dextrose and she woke up immediately.

Clinically she was overweight but otherwise well. Systemic examination revealed no abnormalities.

From the history, Whipple's triad was already satisfied. Nevertheless, it was necessary to exclude other causes of hypoglycemia and demonstrate inappropriately high insulin levels during hypoglycemia.

The results of the extended overnight fast showing plasma glucose and insulin levels are shown in Table 4.

TABLE 4:
CASE 2: RESULTS OF EXTENDED OVERNIGHT FAST SHOWING PLASMA GLUCOSE AND INSULIN LEVELS.

Hours of Fast	12	13	14	15	16½	19½
Plasma Glucose in mg%	38.0	59.0	55.0	36.1	46.0	50.0
Plasma Insulin in mU/L	13.8	22.6	36.1	23.0	20.0	17.5
Insulin/Glucose ratio	0.84	0.38	0.66	0.38	0.43	0.35

To localise the tumor, CT scan of the abdomen was done, but this failed to demonstrate any mass. A coeliac axis angiogram revealed a tumor in the body of the pancreas.

At laparotomy, a tumor was found at the body of the pancreas. It was pedunculated and measured 3 × 2.5 cm. Distal pancreatectomy and splenectomy was done. Intraoperative blood glucose monitoring was also carried out and this showed a rise in blood glucose after pancreatectomy. Histology showed the tumor to be an islet cell adenoma.

Postoperatively, the patient developed hyperglycemia with plasma glucose varying between 200mg% to 300mg%. She required insulin therapy for 1 week. A 75gm glucose tolerance test was done on the 9th postoperative day. The fasting, first and second hour plasma glucose levels were 99mg%, 248mg% and 266mg% respectively.

Her insulin requirements decreased day by day and she was discharged on the 13th postoperative day on a 1,200 calories diabetic diet. A repeat glucose tolerance test 6 weeks later was normal.

On follow up, after discharge, the family reported no further abnormal behaviour. There were no complaints of epigastric pains.

DISCUSSION

The diagnosis of organic hyperinsulinism can often be difficult and requires a high index of suspicion based on repeated episodic alterations in consciousness during the fasting state. It has been reported that the mean duration from initial symptoms to diagnosis was 32.5 months with a range from 10 days to 15 years (1). Our first patient had neuroglycopenia for about 2 years while our second patient was diagnosed after 7 months of symptoms.

A definitive diagnosis of an insulinoma involves 3 stages: (i) Suspicion and confirmation of hypoglycemia as the cause of the patient's symptoms and its relief with correction of hypoglycemia by glucose (Whipple's triad); (ii) Demonstration of an inappropriately high endogenous plasma insulin in the presence of hypoglycemia; (iii) Localisation of the tumor either before or during operation.

Whipple's triad was easily satisfied in our 2 patients. Hypoglycemia can be best provoked by prolonged fasting. More than 90% of all patients with insulinomas can be shown to have hypoglycemia after an overnight fast. In some patients, extension of the fast up to 72 hours or more, coupled with moderate exercise, may be necessary before neuroglycopenic symptoms develop. This is due to habituation to prolonged low blood glucose (2).

The demonstration of an inappropriately high endogenous plasma insulin level is necessary because fasting hypoglycemia can be a feature of other diseases. More important than absolute raised levels of insulin is the inappropriately high insulin level in the presence of low blood glucose levels. An insulin glucose ratio of 0.4 or greater is considered to be diagnostic of insulinoma. Both our patients had such values. The other reported cases of insulinoma in Singapore also satisfy this criteria (3,4).

The self induction of hypoglycemia by the surreptitious administration of insulin and sulphonylurea should always be borne in mind as a differential diagnosis. The measurement of C-peptide concentration (which should be high), should be done if this is suspected. In both our cases, the serum C-peptide levels were not elevated.

The treatment of insulinoma is primarily surgical. In view of the significant morbidity and mortality, accurate localisation of the tumor, either before or during operation, is necessary. Four methods are considered useful: ultrasonography, computerised axial tomography, coeliac axis angiography and portal venous sampling of glucose and insulin levels. These methods were used in the assessment of our patients.

Ultrasonography and computerised tomography give generally poor results as insulinomas are small tumors with sizes ranging from 0.4 cm to 1.8 cm. Both are generally considered to be not helpful, more so ultrasonography (2, 5).

Coeliac axis angiogram has been, and still is, the most widely used technique to localise an islet cell tumor. The percentage ranges from about 50% (5) to about 90% in the series by Fulton from the Mayo Clinic (6). However, Le Quesne (7) and Dagget (8) reported that all tumors localised by angiography can be palpated at surgery and therefore provide an unnecessary information. In addition, false localisation of the tumor can be as high as 20% (5). There is, however, a report by Harrison et al (8) of 2 patients where arteriogram located tumors which could not be palpated.

A technique that is fast becoming a useful method for localisation of insulinoma, especially for occult tumor, was first described by Ingemanssom in 1975, viz percutaneous transhepatic portal venous sampling for plasma glucose and insulin (9). Turner further reported success using the same technique (10). Dagget reported a false localisation of about 62.5% using this technique (5) but attributed this to misinterpretation of the results. He suggested that, to be significant, the insulin level in the venous effluent should be more than 200mU/ml, and to be diagnostic, the insulin level should be more than 500mU/ml. This technique was most accurate in localising the tumor in our first patient.

We have also measured blood glucose intraoperatively as an indication of sufficient excision of the tumor. Although generally considered unreliable (7), nonetheless, it provided useful information in both our patients.

Even after successful removal of the insulinoma, the problems do not end. In a review of 41 patients with insulinoma, Galbut (11) reported peptic ulcer disease in 36%, neuropsychiatric aberration in 28% and diabetes mellitus in 28% of the patients.

Diabetes mellitus as a complication of major pancreatic resection is well known. But even enucleation procedures have been reported to cause diabetes (11). Management of diabetes is along the usual lines, i.e. diet, oral hypoglycemics or insulin. Our second patient had transient diabetes. This was thought to be done to sluggish recovery of the normal islet cells from suppression by prolonged hypoglycemia.

Neuropsychiatric disorders may remain after surgery and is thought to be due to sustained irreversible cerebral damage from hypoglycemia.

The statistically significant increased incidence of peptic ulcer disease manifesting as pain or bleeding was postulated to be due to hypergastrinism but this is not proven. It is interesting that Hardy and Doolittle (12) reported 2 cases in whom Zollinger-Ellison Syndrome developed subsequently.

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