

# BENIGN INSULINOMA – A DIAGNOSTIC CHALLENGE: A CASE REPORT

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## SUMMARY

*A 22-year-old Malay man with recurrent hypoglycaemic fainting spells was found to have hyperinsulinism. Although the CT-scan of the abdomen and arteriogram failed to demonstrate any tumour in the pancreas, three tumours were found in the body of the pancreas at laparotomy. An appraisal of the techniques currently available for diagnosis and localisation of insulinoma is presented.*

## INTRODUCTION

Organic hyperinsulinism has to be managed step-by-step. The first step is the demonstration of Whipple's triad, *viz*: symptoms precipitated by fasting or exercise; hypoglycaemia during symptoms; and relief of symptoms by glucose.

The second step is the demonstration of endogenous plasma insulin levels inappropriate to the prevailing glucose level, and the third step is localising the tumour preoperatively. Finally, an operation should be done to relieve the symptoms. Each step has its own pitfalls making the management difficult. The case described illustrates these problems.

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## CASE REPORT

A 22-year-old man who had served national service uneventfully three years ago lost consciousness one morning during reservist training during the fasting month. As it was the fasting month for Muslims, he was not given any breakfast that morning. He was brought to the medical centre, where after taking blood for glucose estimation, glucose was given, resulting in recovery of consciousness. He was then referred to hospital. On admission, he revealed that about a year previously, he was, during similar military training, unarousable in the morning after overnight training. He regained consciousness, after an injection at the medical centre. Since that day he had at least six similar episodes.

Each time, usually after returning home late to a light dinner, he would sleep through lunch and sometimes dinner. Whenever this happened, his mother would feed him biscuits and honey and he would wake up. He found that he could prevent such episodes by taking a heavy supper. He did not complain of palpitations, sweatiness or tremor. His family however, noticed that in the last few months his behaviour was odd. Over the past year, his weight had increased by 8 kg.

Clinical examination was unremarkable. The plasma glucose taken at the medical centre was analysed and found to contain less than 30 mg glucose/100 mls. The morning after admission he was

unconscious. There were no signs of increased sympathetic activity such as sweatiness, tachycardia or hypertension. Plasma glucose then was 11 mg%. He responded promptly to intravenous glucose administration.

After overnight fasting, plasma glucose and insulin were assayed (Table I).

Serum calcium and phosphate levels were normal. Plasma cortisol showed a normal circadian rhythm.

To localise the tumour, a CT scan of the abdomen was performed; it was normal. Angiography failed to demonstrate any tumour. An exploratory laparotomy was proposed but the patient refused operation. He was started on oral diazoxide 800 mg/day in divided dose and the pre-breakfast blood sugar was 55 mg/100 mls. The hypoglycaemia attacks, though less frequent, were still present and he finally agreed to surgery.

As pre-operative localisation was unsuccessful, laparotomy was performed with intra-operative monitoring of plasma glucose at five-minute intervals. Prior to the laparotomy, plasma glucose was maintained at 50 mg% by infusion of 5% Dextose at a constant rate, to avoid hypoglycaemia during anaesthesia.

Three tumours were found: the first on anterior surface of the head of the pancreas measuring 1.5 cm in diameter, two others of 1 cm and 2 cm in diameter were found in the body of the pancreas. The regional lymph nodes and liver were free of metastasis. The blood glucose level rose to 88 mg% five minutes after

removal of the first tumour. Glucose infusion was stopped at this stage. After removal of the second and third tumours (partial pancreatectomy), the blood glucose remained at around 80 mg% without glucose infusion. Six islet cell tumours were seen under microscopy, the smallest being 0.5 mm in diameter with no evidence of vascular invasion. Post-operatively, patient had mild transient hyperglycaemia. He has been well since the operation.

## DISCUSSION

This case illustrates the difficulties involved during the work-up of a case of insulinoma. By the time the patient was admitted to hospital, enough data had been gathered to fulfill Whipple's triad, otherwise, the best provocative test is a prolonged fast up to 72 hours. The next step is to demonstrate inappropriate insulin secretion in the presence of hypoglycaemia. To this end, simultaneous measurement of plasma insulin and plasma glucose after an overnight fast was performed. An inappropriately high ratio of plasma immunoreactive insulin to glucose ( $> 0.3$ ) was obtained and this is a reliable diagnostic feature of insulinoma.<sup>2</sup> Such inappropriate secretion can also be seen in patients with factitious hypoglycaemia.

Determination of plasma C-peptide and proinsulin during a suppression test with intravenous fish insulin would show little detectable C-peptide (0.03 pmol/ml) or pro-insulin (0.1 pmol/ml)<sup>3</sup> in patients with factitious hypoglycaemia. Highly purified insulin could be used in place of fish insulin. Unfortunately C-peptide and proinsulin are not yet available locally. Measurement of non-specific tumour markers, particularly human chorionic gonadotropins (HCG) and its subunits is useful in patients with malignant islet cell tumours<sup>4</sup> but again was not performed because of inavailability.

The most useful localisation procedure is arteriography which shows a hypervascular mass or displacement of pancreatic arteries in 60 to 70% of the cases.<sup>5,6</sup> The success of selective arteriography in localising tumours depends on the size of the tumour (preferably  $> 3$ cm).<sup>2</sup> CT scanning is much less helpful since it is positive in only 20% of the cases. Ultrasound study is positive even less

TABLE I  
CHANGES IN PLASMA GLUCOSE AND  
INSULIN LEVELS WITH TIME

Time (a.m.)	Glucose (mg/100 ml)	Plasma Insulin (mu/L)	Insulin: Glucose ratio
7	32	61.2	1.9
8	31	49.7	1.6
9	34	40.7	1.2
10	26	46.5	1.8

frequently. When arteriography and computerised tomography have not demonstrated a suspected insulinoma, selective transhepatic pancreatic vein sampling for immunoreactive insulin has been reported to detect lesions smaller than 1 cm.<sup>8,9</sup> Because of the hazardous nature of this procedure, it was not considered for this patient. As tumours have been found at the time of operation in over 75% of patients with biochemical evidence of islet-cell lesions without the use of angiographic examination,<sup>10</sup> it was not unreasonable to subject this patient to surgical exploration without further attempts at pre-operative localisation. Intraoperative monitoring of peripheral venous glucose levels to confirm successful excision of insulinoma was organised but as it turned out was superfluous in this patient. Nevertheless, the experience from Mayo Clinic is that this method is not completely reliable.<sup>11</sup>

The diagnosis of insulinoma is not a new problem. In the local context, in 1974 Singh<sup>12</sup> reported a case diagnosed by means of selective angiography, while Teh<sup>13</sup> in 1982 had success using angiography and computerised tomography. The present case described is unique in that while pre-operative localisation of tumour was unsuccessful, surgical exploration revealed multiple adenomata. It is a reminder that pre-operative tumour localisation, while ideal, may not always be possible or required.

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