

A Rare Cause of Syncope in a Patient with Diabetes Mellitus—A Case Report

S Tavintharan,**FAMS, MBBS, MRCP (UK)*, J J Mukherjee,***FAMS, MBBS, MRCP (UK)*

Abstract

Introduction: Hypoglycaemic episodes in patients with diabetes mellitus are mostly due to excess doses of exogenous insulin or oral hypoglycaemic agents, coupled with poor caloric intake and excessive unplanned physical exertion. Hypoglycaemia as a result of endogenous hyperinsulinaemia due to an insulinoma is extremely rare in such patients. **Clinical Picture:** This patient with type 2 diabetes mellitus presented with episodes of syncope. Investigations confirmed recurrent hypoglycaemia from endogenous hyperinsulinaemia, with localisation of a tumour in the tail of the pancreas. **Treatment:** Distal pancreatectomy and splenectomy. Histology confirmed an insulinoma. **Outcome:** No further hypoglycaemic episodes were noted. The patient returned to his diabetic state with rather poor glycaemic control. **Conclusions:** Repeated hypoglycaemic episodes in a patient with diabetes mellitus despite complete withdrawal of hypoglycaemic agents should lead one to consider other causes of hypoglycaemia.

Ann Acad Med Singapore 2001; 30:436-9

Key words: Diabetes mellitus, Endogenous hyperinsulinaemia, Hypoglycaemia, Insulinoma

Introduction

Hypoglycaemia is a common medical emergency. It presents either with symptoms of neuroglycopenia, such as episodes of visual blurring, confusion, convulsions and sometimes coma or with symptoms caused by excess of counterregulatory hormones like catecholamines, such as palpitations, sweating and tremulousness.¹ It is most commonly seen in patients with diabetes mellitus, but can also occur in patients with renal failure, liver disease, malnutrition, congestive cardiac failure, severe sepsis or cancer. Surreptitious use of insulin or sulphonylurea is probably the most common cause of hypoglycaemia in non-diabetic patients.² Occasionally, tumours can induce hypoglycaemia: either pancreatic insulinomas or non-islet cell tumours like fibromas and fibrosarcomas secreting insulin-like growth factors.^{3,4}

Amongst the tumours causing hypoglycaemia, insulinomas by far are the most common ones.⁵ They are commonly seen during the fourth to sixth decades of life and are equally distributed between both the sexes.⁶ The incidence has been estimated to be four cases per million per year.⁷ More than 99% of them occur in the substance of the pancreas, with the rare ectopic insulinomas occurring in the wall of the duodenum, ileum and porta hepatis.⁸

Although it is well documented that about 10% of patients with insulinoma develop diabetes mellitus postoperatively,⁸ it is extremely uncommon for a patient with pre-existent diabetes mellitus to harbour an insulinoma. So far, only about 20 patients with such a combination have been reported in the literature. We describe a patient with type 2 diabetes mellitus who developed hypoglycaemia due to unequivocal endogenous hyperinsulinaemia, with an alleviation of the hypoglycaemic episodes following the successful surgical excision of an insulinoma.

Case Report

A 51-year-old Chinese male was diagnosed to have type 2 diabetes mellitus 4 years ago by his general practitioner, based on elevated fasting and random blood glucose levels. He was commenced on oral hypoglycaemic agents and was on regular follow-up till about 1 year prior to his admission. For the past 1 year prior to this admission, he defaulted follow-up with the general practitioner, stopped taking his oral hypoglycaemics, was not at all compliant with the dietary restrictions and yet had no symptoms of polyuria or polydipsia.

He was admitted with complaints of episodic fainting, drowsiness and sweating of 4 weeks' duration. These

* Associate Consultant
Department of Medicine
Changi General Hospital

** Consultant
Division of Endocrinology
Department of Medicine
National University Hospital

Address for Reprints: Dr J J Mukherjee, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

symptoms were associated with hunger and resolved after a meal. In addition, he was involved in a minor road traffic accident 1 week prior to the admission when he had lost consciousness while riding on his motorcycle. However, he did not seek any medical attention then. Apart from the past history of type 2 diabetes mellitus, he had no other significant history of note. He does not consume alcohol and was not consuming any western or traditional medication prior to admission.

Clinical examination revealed an overweight male with a body mass index (BMI) of 29.4 kg/m². His pulse was 84/min, regular. Blood pressure was 130/80 mmHg in a supine position with no postural drop. There was no pallor. There were no signs suggestive of chronic liver disease. Cardiovascular, respiratory, abdominal and neurological examination was normal. There was no clinical evidence of diabetic vascular disease, peripheral neuropathy or retinopathy.

Plasma glucose level on admission was 2.2 mmol/L and he had four further episodes of documented hypoglycaemia with the plasma glucose values below 2.2 mmol/L, each episode being associated with symptoms of hunger and giddiness. Simultaneous insulin and C-peptide levels were measured twice and were suggestive of endogenous hyperinsulinaemia:

Plasma glucose (mmol/L)	Fasting insulin (mU/L) (Normal range <5 mU/L)	Fasting C-peptide (ug/L) (Normal range <1.0 ug/L)
1.9	95	13.5
1.3	152	15.8

The glycosylated haemoglobin level was 5.3%. Urea and electrolytes were normal as was the liver function test. The blood and urine toxicology screen for all the commonly used oral hypoglycaemic agents was negative.

Computed tomography (CT) of the abdomen revealed a solitary tumour measuring 2.3 cm in diameter in the tail of the pancreas. The rest of the pancreas, liver, spleen, kidneys and adrenals were noted to be normal on the scan.

A baseline screen for the rare possibility of Type 1 multiple endocrine neoplasia including measurement of serum calcium, serum prolactin and serum cortisol was normal.

Preoperatively, despite having regular meals, he required infusion of 500 mL of 10% dextrose every eight hours to prevent hypoglycaemia. He underwent a distal pancreatectomy and splenectomy 3 weeks following his admission. Peroperatively, he was noted to have a 1.7 cm diameter, firm and well circumscribed yellow nodule in the tail of the pancreas. Histological examination confirmed the nodule to be a pancreatic endocrine tumour, with no evidence of tumour emboli or perineural infiltration.

Immunostaining was positive for insulin and somatostatin but negative for glucagon and gastrin. The patient was administered pneumococcal vaccine consequent upon the splenectomy.

Postoperative recovery was unremarkable. The hypoglycaemia resolved and his fasting plasma glucose 2 days postoperatively ranged between 9 and 11 mmol/L. He was discharged with dietary advice for a restricted 1800 kilocalorie diabetic diet.

On follow-up at 3 months, his blood sugars were noted to be inadequately controlled on dietary therapy alone, with the glycosylated haemoglobin levels being elevated at 11.9%. A C-peptide stimulation test with 1 mg intravenous glucagon showed adequate levels of C-peptide at 1.9 ug/L at 0 minutes and 2.9 ug/L at 6 minutes. He was commenced on oral hypoglycaemic agents. However, 12 months following the excision of the insulinoma, his glycaemic control, despite showing good improvement, continues to remain poor with the glycosylated haemoglobin level elevated at 8.3% on 500 mg thrice daily of metformin and tolbutamide. Moreover, he was also noted to have developed diabetic nephropathy, as evidenced by microalbuminuria and background diabetic retinopathy. He was started on an angiotensin converting enzyme inhibitor, enalapril, and the dose of tolbutamide was doubled. He is due for another review of his glycaemic control in 3 months time with a view to further intensifying his therapy should the glycosylated haemoglobin level continues to remain above 7%.⁹

Discussion

Insulinoma is an uncommon tumour. The median age at diagnosis is 50 years in sporadic cases and 23 years in patients with multiple endocrine neoplasia, type 1 (MEN 1).^{10,11} Insulinomas are usually small in size, average 1 to 2 cm in diameter, with some as large as 15 cm. About 10% of insulinomas are malignant; a diagnosis that cannot be made by histopathological examination alone but requires the presence of documented metastatic deposits. The risk of harbouring a malignant insulinoma is higher in those with MEN1 (21% at 10 and 20 years) than in those without MEN 1 (5% at 10 and 7% at 20 years).⁷

The relationship between diabetes mellitus and insulinoma is intriguing. A strong association between insulinoma and familial incidence of diabetes mellitus has been documented in several reports.^{12,13} In a series of patients with insulinomas seen at Mayo Clinic, about 30% had a positive family history of diabetes mellitus.¹³ However, on the other hand, insulinoma in a patient with pre-existent diabetes mellitus is extremely rare. Hypoglycaemic episodes in patients with diabetes mellitus are mostly due to excess doses of exogenous insulin or oral hypoglycaemic agents.

An insulinoma in such patients presents a diagnostic as well as a therapeutic challenge.

Kane et al¹⁴ described a functioning insulinoma in a patient with type 2 diabetes mellitus and reviewed the history of the patients with histologically proven insulinoma over a period of 65 years at the Mayo clinic. Out of the 313 confirmed cases till 1993, they could find only 1 patient with coexistent insulinoma and pre-existent diabetes mellitus. Svartberg et al,¹⁵ in a report in 1996, described the only patient with type 1 diabetes mellitus with a coexistent insulinoma. They reviewed the literature and noted that there were only 17 previous reports of well-documented functioning insulin producing tumours in patients with type 2 diabetes mellitus. The diagnosis in 8 of these 17 patients was made at autopsy, 5 being discovered accidentally. In only 3 of these 8 patients was the diagnosis of an insulinoma suspected prior to the patient's death. In the other 9 patients, the diagnosis was suspected before surgery and after the operation, all patients either returned to a diabetic state or had an increase in blood sugar levels. Eleven of these 17 patients had a solitary β -cell adenoma, 4 had malignant insulinomas, 1 had multiple β -cell adenomata and 1 had an adenoma in ectopic pancreatic tissue.

Our patient was diagnosed to have type 2 diabetes mellitus 4 years prior to the diagnosis of the insulinoma. Although previous records were not available, our patient was certain of the diagnosis which was made after he had consulted a general practitioner for thirst and polyuria and remembered being on oral medication and being seen by the general practitioner once every 2 to 3 months when he had capillary blood checked for glucose. However, he defaulted follow-up after about 3 years, and was not on any long-term medication for a year preceding the admission with hypoglycaemia. It is conceivable that the development of insulinoma could have kept his blood glucose and hence symptoms of polyuria and polydipsia at bay despite him having stopped his oral hypoglycaemics and resorting to diet containing refined sugars. There was no doubt about the existence of endogenous hyperinsulinaemia. He had inappropriately elevated insulin and C-peptide levels in the presence of hypoglycaemia. In patients in whom the diagnosis is suspected, a plasma insulin (uU/mL) to glucose (mg/dL) ratio of greater than 0.3 when blood glucose is 2.2 mmol/L (40 mg/dL) or less is diagnostic of endogenous hyperinsulinaemia.¹⁶ The ratio was 4.4 in our patient. With rare exceptions, insulin-mediated hypoglycaemic disorders are characterised by a plasma insulin concentration of 6 uU/mL or higher, when plasma glucose is 50 mg/dL (2.8 mmol/L) or less, whereas in persons with non-insulin mediated hypoglycaemic disorders the insulin concentration is 5 uU/mL or less.¹⁷ Our patient had unusually high levels

of insulin and C-peptide and this suggests that he had a degree of insulin resistance.

The CT scan showed a definite lesion in the tail of the pancreas in our patient and thus further imaging and localising tests were not required. CT scanning and magnetic resonance imaging (MRI) are usually the first-line imaging modalities employed for the localisation of an insulinoma and give a detection rate in experienced centres from 45% to 75%.¹⁸ Although preoperative abdominal ultrasonography is of little value in the localisation of an insulinoma, intraoperative ultrasonography has high sensitivity and specificity.^{19,20} The results with somatostatin receptor scintigraphy are unsatisfactory, as only about 50% of insulinomas carry the somatostatin receptor.²¹ Zimmer et al²¹ studied the relative ability of CT, MRI, abdominal ultrasonography, somatostatin receptor scintigraphy and endoscopic ultrasonography in the localisation of the primary tumour in 10 patients with surgically resected and histologically proven insulinoma. The sensitivities were reported as 93% with endoscopic ultrasonography, 21% with CT, 14% with somatostatin receptor scintigraphy, and 7% with MRI and abdominal ultrasonography.

Following successful surgery, the blood glucose values in our patient soared into the diabetic range and the glycosylated haemoglobin level rose from 5.3% to 11.9% within 3 months. The C-peptide stimulation test demonstrated adequate insulin reserve, thus confirming that the diabetic state postoperatively was due to underlying insulin resistance rather than insulin insufficiency. Our patient thus satisfies all the five criteria for the diagnosis of a functioning insulinoma in a patient with diabetes mellitus as suggested by Sandler et al²²: development of fasting hypoglycaemia, evidence that hypoglycaemia was not caused by exogenous administration of insulin, exclusion of other causes of hypoglycaemia, presence of endogenous hyperinsulinaemia and amelioration of hypoglycaemia by removal of the neuroendocrine pancreatic tumour.

Conclusion

Hypoglycaemia is a medical emergency and its diagnosis requires a high index of suspicion. Once considered, the diagnosis is easy to establish and simple to treat with a remarkable response in the symptoms and signs. In patients with diabetes mellitus, hypoglycaemia is often a result of excess doses of exogenous insulin or oral hypoglycaemic agents, coupled with poor caloric intake and excessive unplanned physical exertion. However, repeated hypoglycaemic episodes even after complete withdrawal of the hypoglycaemic agent should lead to a search for other causes of hypoglycaemia. An insulinoma in such a situation remains a rare possibility, which once diagnosed, yields a rewarding chance of cure.

REFERENCES

1. Towler D A, Havlin C E, Craft S, Cryer P. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 1993; 42:1791-8.
2. Roith D L. Tumor-induced hypoglycemia. *N Engl J Med* 1999; 341: 757-8.
3. Service F J. Hypoglycemic disorders. *N Engl J Med* 1995; 332:1144-5.
4. Koch C A, Rother K I, Roth J. Tumour hypoglycemia linked to IGF-II. In: Rosenfeld R, Roberts C T, editors. *Contemporary Endocrinology: The IGF-II System*. Totowa NJ: Humana Press, 1999:675-98.
5. Vinik A I, Thompson N W, Averbuch S D. Neoplasms of the gastroenteropancreatic endocrine system. In: Holland J F, Frei III, Bast R C, Kufe D W, Morton D L, Weichselbaum R R, editors. *Cancer Medicine*. Philadelphia: Lea and Feiberger, 1993; XXVI-5:1180-209.
6. Stefanini P, Carboni M, Patrassi N. Surgical treatment and prognosis of insulinoma. *Clin Gastroenterol* 1984; 3:697-709.
7. Service F J, McMahon M M, O'Brein P C, Ballard D J. Functioning insulinoma—incidence, recurrence, and long-term survival of patients. *Mayo Clinic Proc* 1991; 66:711-9.
8. Cryer P E, Polonski K S. Glucose homeostasis and hypoglycemia: management of insulinoma. In: Wilson J D, Foster D W, Kronenberg H M, Larsen P R, editors. *Williams Textbook of Endocrinology*. Philadelphia: WB Saunders, 1992:1241.
9. UKPDS Group. Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837-53.
10. Perry R R, Vinik A I. Diagnosis and management of functioning islet cell tumours. *J Clin Endocrinol Metab* 1995; 80:2273-8.
11. Norton J A, Whitman E D. Insulinoma. *Endocrinologist* 1995; 3: 258-67.
12. Marks V, Samols E. Insulinoma: natural history and diagnosis. *Clin Gastroenterol* 1974; 3:559-73.
13. Priestly J T. Hyperinsulinism. *Ann R Coll Surg Engl* 1962; 31:211-27.
14. Kane L A, Grant C S, Nippoldt T B, Service F J. Insulinoma in a patient with NIDDM. *Diabetes Care* 1993; 16:1298-300.
15. Svaberg J, Stridsberg M, Wilander E, Andersson D E, Eriksson B. Tumour-induced hypoglycaemia in a patient with insulin-dependent diabetes mellitus. *J Intern Med* 1996; 239:181-5.
16. Fajans S S, Floyd J C. Fasting hypoglycaemia in adults. *N Engl J Med* 1976; 294:766-72.
17. Service F J, Dale A J, Elveback L R, Jiang N S. Insulinoma: clinical and diagnostic features of 60 consecutive cases. *Mayo Clin Proc* 1976; 51:417-29.
18. Clark L R, Jaffe M H, Choyke P L, Grant E G, Zeman R K. Pancreatic imaging. *Radiol Clin North Am* 1985; 23:489-501.
19. Fraker D L, Norton J A. Localization and resection of insulinomas and gastrinomas. *JAMA* 1988; 259:3601-5.
20. Norton J A, Shawker T H, Doppman J H, Fraker D L, Cromack D T, Gordon P, et al. Localization and surgical treatment of occult insulinomas. *Ann Surg* 1990; 212:615-20.
21. Zimmer T, Stolzel U, Bader M, Koppenhagen K, Hamm B, Buhr H, et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localization of insulinomas and gastrinomas. *Gut* 1996; 39:562-8.
22. Sandler R, Horwitz D L, Rubenstein A H, Kuzuya H. Hypoglycemia and endogenous hyperinsulinism complicating diabetes mellitus. Application of the C-peptide assay to diagnosis and therapy. *Am J Med* 1975; 59:730-6.