Hypoglycaemia following removal of phaeochromocytoma: case report and review of the literature

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Summary

Hypoglycaemia may complicate removal of a phaeochromocytoma, but its pathogenesis is not well understood. The sixth such case in the world literature is reported together with details of glucose tolerance testing and hormone levels before and after extirpation of an adrenal phaeochromocytoma. The mechanism of hypoglycaemia probably relates to a sudden decrease in circulating catecholamines which allows a rebound increase in insulin release and in peripheral glucose uptake. It is suggested that blood sugar levels should be monitored routinely after surgery for phaeochromocytoma.

Introduction

There have been only 5 reported cases of hypoglycaemia following removal of a phaeochromocytoma, and this complication is not mentioned in the comprehensive textbook by Manger and Gifford (1977). In this report we review the literature and describe a sixth case along with details of glucose, insulin, C-peptide, glucagon and catecholamine levels before and after resection of an adrenal phaeochromocytoma.

Case report

A 59-year-old forestry worker presented to this hospital because of poor control of diabetes mellitus. Diabetes had been diagnosed 6 months before when treatment was initiated with an oral hypoglycaemic agent. He subsequently suffered attacks of hunger, sweating and weakness which were attributed to hypoglycaemia although blood glucose levels were always normal or elevated. Questioning revealed a 3

year history of exertional headache and 2 years of intermittent hypertension. For 6 months he had noted increasing constipation and a 12-kg weight-loss.

On examination positive findings were a fine tremor, cool moist skin, blood pressure 198/98 mmHg supine, 194/112 mmHg standing, arterio-venous nipping in the fundi, and a third heart sound gallop rhythm.

Biochemical testing confirmed the diagnosis of phaeochromocytoma (Table 1). Plasma levels of noradrenaline, adrenaline and dopamine (Peuler and Johnston, 1977) were elevated as was the urinary excretion of catecholamines, vanillyl-mandelic acid (VMA) and total metanephrines. Treatment was initiated with labetalol, increasing from 400 mg to 900 mg daily which normalized blood pressure. A computed tomographic (CT) scan showed a 5 cm-diameter mass above the left kidney. The premedication for anaesthesia was pethidine, promethazine, and phenoperidine. The patient was given an epidural anaesthetic at the level of T-8. General anaesthesia was induced with thiopentone and diallonortoxiferine and maintained with nitrous oxide. At operation a tumour (6×5×4 cm) arising from the left adrenal was found and removed along with the adrenal gland. Before removal of the tumour, arterial pressure was controlled by intermittent infusions of labetalol and nitroprusside. During the operation the patient received a total of 1500 ml of stable plasma protein solution (SPPS), 350 ml of 5% dextrose and 600 ml of 4.3% dextrose and 0.18% saline mixture. He returned to the recovery room with infusions of SPPS and 5% dextrose, and consciousness was regained some 15 min later. The dextrose infusion was stopped and the patient was given two units of whole blood. Approximately 2½ hr after completion of surgery he became sweaty, unrousable and developed a tachycardia. A blood sample drawn urgently showed

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TABLE 1. Catecholamine and metabolite levels before and after removal of a phaeochromocytoma*

Plasma	Noradrenaline	Adrenaline	Dopamine
	(150–800 pg/ml)	(15–120 pg/ml)	(20–150 pg/ml)
Pre-surgery	2287	2026	803
Post-surgery	792	74	–
Urine	Catecholamines	VMA ratio	Total metanephrines
	(<0.6 µmol/24hr)	(1.58–2.25)	(<1.0 mg/24hr)
Pre-surgery	7.1	1.05	3.6
Post-surgery	0.41	1.95	0.26

*Normal values are shown in parentheses.

hypoglycaemia (plasma glucose 1.9 mmol/litre). His clinical state improved dramatically after the administration of 50 g glucose intravenously. He was maintained on an infusion of 4.3% dextrose and 0.18% saline at 60 ml/hr and had no further episodes of hypoglycaemia. The plasma glucose remained above 3.5 mmol/litre.

Arterial pressure was normal after surgery and catecholamines and metabolite levels fell to normal levels (Table 1). The tumour showed typical features of a phaeochromocytoma on histological examination.

Additional studies

A 25 g intravenous glucose tolerance test was performed before surgery (4 days after commencing labetalol treatment) and again 14 days post-surgery off all medications. Along with glucose, blood samples were drawn for insulin (Scott *et al.*, 1980), C-peptide (Scott *et al.*, 1980) and glucagon estimations (Aguilar-Parada, Eisentraut and Unger, 1969). Glucagon was measured using a highly specific antiserum (M107). As shown in Fig. 1, fasting plasma glucose was elevated (9.6 mmol/litre) presurgery and glucose disposal was markedly impaired (disposal constant, Kg, 0.47, normal >1.2). Plasma insulin and C-peptide levels were inappropriately low and showed no response to hyperglycaemia. After surgery, the fasting glucose level and the Kg values returned to normal and there was a dramatic increase in the response of both insulin and C-peptide to glucose loading (Fig. 1). Fasting plasma glucagon was raised before surgery and showed little response to intravenous glucose. In contrast, the fasting value was normal post-surgery and a normal decrement occurred in response to hyperglycaemia.

Discussion

Hypoglycaemia following removal of a phaeochromocytoma has been reported in 5 previous cases, details of which are listed in Table 2. Apart from the

present case, none was clearly diabetic before surgery. Hypoglycaemia was diagnosed within 2½ hr of completion of surgery in all patients despite the concurrent administration of intravenous glucose solutions in at least two instances (patients 1 and 2, Table 2). In only one instance (Patient 2) was insulin measured at the time of hypoglycaemia and in this case an inappropriately high level of plasma insulin was found. All patients responded well to concentrated glucose solutions and no recurrence of hypoglycaemia was documented.

Why transient hypoglycaemia should occur in some patients remains unclear but the sudden removal of the inhibitory effect of catecholamines on insulin secretion is likely to play a major part. Studies involving short term infusions of adrenaline in normal man have shown rebound hyperinsulinism, inappropriate in relation to the prevailing plasma glucose concentration, when infusions are terminated (Porte *et al.*, 1966). The inhibitory effect of alpha-adrenergic stimulation on insulin secretion can also be rapidly reversed by alpha-adrenergic blocking drugs (Turnbull *et al.*, 1980). In our patient the dramatic improvement in the ability to release insulin during glucose loading after removal of the phaeochromocytoma is consistent with these studies. Other possible contributions to hypoglycaemia include enhanced peripheral glucose uptake and/or diminished hepatic glucose output, independent of change in insulin secretion. Catecholamines have been shown to inhibit glucose uptake (Ellis, 1959) and it is possible that this effect is rapidly reversed after the resection of the tumour. Depletion of liver glycogen by high levels of adrenaline and glucagon before and during surgery may also contribute to hypoglycaemia. Short-term adrenaline infusions stimulate glucagon in normal man (Gerich *et al.*, 1974) and it is interesting to note that inappropriately high levels of glucagon observed presurgery were normalized in our patient after surgery. Finally an effect of epidural anaesthesia on the normal defence mechanism against hypoglycaemia cannot be dismissed. Neural afferent blockade

TABLE 2: Peri-operative data on six male patients with hypoglycaemia

Author	No./Age	Pre-surgery blood glucose (mmol/litre)	Drugs	Fluids	Onset of hypoglycaemia post surgery	Blood glucose (mmol/litre)
Martin, St Pierre and Moliner (1979)	1/21	6.38 (Random)	Pre-surgery Phentolamine Phenoxybenzamine Propranolol During surgery Phentolamine	Pre-surgery 5% Dextrose 1 litre over 2hr 40 min Post-surgery 125ml/hr	40 min	1.88
Wilkins, Schmidt and Doll (1977)	2/52	9.4 (Random) 7.2 (Fasting)	Pre-surgery Phenoxybenzamine	During surgery 5% dextrose 250ml/hr Post-surgery 50ml/hr	2 hr	0.99
	3/12	4.7 (Random) 7.1 (2 hr after food)	Pre-surgery Phenoxybenzamine	During surgery 5% dextrose 700 ml 2½ hr	30 min	1.6
Allen and Imrie (1977)	4/60	7.8 (Random)	Pre-surgery Phenoxybenzamine Propranolol During surgery Propranolol	During surgery 5% dextrose 1.5 litre	2hr	1.9
Sagalowsky and Donohue (1980)	5/50	6.1 6.4 (Random)	Pre-surgery Dibenzyliline	During surgery 5% dextrose over 6 hr	Coma at end of anaesthetic	1.9
Chambers (1982)	6/54	9.5 (Fasting)	Pre-surgery Labetolol During surgery Labetolol	During surgery 5% dextrose 350ml 4.3% dextrose 600ml	2½ hr	1.9

has been shown to attenuate the expected stress-induced rise in cortisol (Engquist *et al.*, 1977) growth hormone (Brandt *et al.*, 1976) and catecholamines (Halter and Pflug, 1980)—all of which are concerned with the counter regulatory effects of insulin-induced hypoglycaemia.

The effect of alpha and beta blocking drugs on glucose homeostasis is complex and difficult to assess in patients with phaeochromocytoma. All patients listed in Table 2 received alpha blocking agents which would be expected to increase the insulin response to glucose. Since beta blocking drugs would tend to inhibit insulin secretion, these drugs have been recommended in the peri-operative period to protect against hypoglycaemia (Sagalowsky and Donohue, 1980). Clearly, labetalol, a drug with mainly beta blocking activity, failed to protect against hypoglycaemia in the present case.

In conclusion, there are good physiological reasons why hypoglycaemia may occur after removal of phaeochromocytoma. The complication will not necessarily be prevented by standard glucose infusions. Signs of hypoglycaemia may be masked by beta-

adrenergic blocking drugs and the diagnosis should be suspected in any patient who fails to gain consciousness or who loses consciousness in the early post-surgery period. In addition to glucose infusions we recommend that blood glucose levels should be measured as soon as the patient reaches the recovery room and at least once in the subsequent three hours in all patients after surgery for a phaeochromocytoma.

Acknowledgments

Grant support was from the Medical Research Council of New Zealand. We thank Dr Russell Scott for allowing us to study his patient, Mrs Carolyn Redekopp for glucagon assays and Mrs Natalie Purdue for typing the manuscript.

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FIG. 1. Plasma levels of glucose, insulin, c-peptide and glucagon in response to a 25 g i.v. bolus of glucose before (○) and after (●) removal of a pheochromocytoma. The Kg values were 0.47 before and 1.59 after surgery.

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