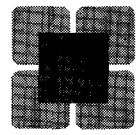

Diabetic ketoacidosis associated with pheochromocytoma

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■ A 29-year-old woman was found to have diabetic ketoacidosis associated with classic findings of pheochromocytoma, an association previously undescribed. The patient also had a significant insulin requirement that resolved after tumor excision. Pheochromocytoma with associated hyperglycemia and glycosuria has been reported since 1912, but ketoacidosis has been thought not to occur with pheochromocytoma. The findings in this case are described, and glucose metabolism in pheochromocytoma is reviewed.

□ INDEX TERMS: KETOSIS, DIABETIC; ACIDOSIS, DIABETIC; PHEOCHROMOCYTOMA □ CLEVE CLIN J MED 1992; 59:423–427

HYPERGLYCEMIA and glycosuria associated with pheochromocytoma have been reported since 1912,[1] but it has been traditionally taught that ketoacidosis does not occur with pheochromocytoma.[2,3] We report a patient who had classic findings of a pheochromocytoma with associated ketoacidosis, and a significant insulin requirement that resolved with tumor excision.

CASE REPORT

A 29-year-old black female first sought medical attention for daily pounding headaches and palpitations. She had been in excellent health except for an episode of fever and arthralgias, diagnosed as rheumatic fever, at the age of 9. She had had four pregnancies, all of which went to term, with normal vaginal deliveries. The babies' birth weights ranged from 6 to 7.5 lb. There was no evidence for gestational diabetes. Personal or family history was negative for hypertension, diabetes mellitus, or other endocrine abnormalities.

Her physical examination was normal: blood pressure was 94/60 mm Hg, and heart rate was 76 beats per minute (bpm). She weighed 101.4 lb. Migraine headache was diagnosed after an interviewer elicited a history of an aura, and she was treated with Fiorinal (butalbital, aspirin, and caffeine). Her headaches persisted, and 2 months later, after visiting the emergency room on 5 consecutive days, she was admitted to the hospital. Her physical exam was unchanged: her blood pressure remained low, and electrolytes, glucose, blood urea nitrogen, creatinine, and complete blood count were all within normal limits. She was chemically euthyroid and had a normal serum cortisol level. Lumbar puncture, sella turcica radiography, and computed tomography (CT) scan of the head were unremarkable. Neuropsychiatric evaluation revealed no hypochondriasis, anxiety, or depression, and she was dis-

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TABLE
PRE- AND POSTOPERATIVE CATECHOLAMINE LEVELS

	Urine					Plasma		
	NE (mg/tv)	EPI (mg/tv)	DA (mg/tv)	VMA (mg/tv)	META (mg/tv)	NE (pg/mL)	EPI (pg/mL)	DA (pg/mL)
Pre-op	1798	4701	5890	42.0	6.5	11577	29195	2360
Post-op								
Immediately	58	410	746	4.4	–	–	–	–
6 months	42	29	425	6.0	–	130	20	<40
8 months	17	18	358	–	<0.1	–	–	–
18 months	23	14	372	3.7	<0.1	–	–	–
Normal	<100	<30	<300	≤10	≤1.0	213±60	28±16	<300

NE, norepinephrine; EPI, epinephrine; DA, dopamine; VMA, vanillylmandelic acid; META, metanephrines; tv, total volume

charged with the presumed diagnosis of vascular headaches.

Two years later she presented once again to the emergency room. She had avoided medical attention in the interim, but her headaches had become increasingly severe and were now associated with nausea, vomiting, chest pain, shortness of breath, episodes of shaking, and right upper quadrant abdominal pain. She could not sleep or eat solid food and had lost 10 lb in 1 month. She suffered from polyuria, heat intolerance, visual blurring, excessive forehead perspiration, epigastric discomfort, rapid palpitations with the development of a "sticky sensation in her chest" and a fullness or lump in her throat. She also complained of cold hands and feet, occasional dyspnea on exertion, two-pillow orthopnea, paroxysmal nocturnal dyspnea, pallor, and tremulousness.

She was now hypertensive (blood pressure 160/110 mm Hg) with 50 mm Hg of orthostasis. Mild nonspecific right upper quadrant abdominal tenderness was noted; the physical exam was otherwise unremarkable. Electrolytes were still within normal limits, but serum glucose was 277 mg/dL (15.4 mmol/L) (normal, 70 to 112 mg/dL). Hematocrit was 46%, with a white blood count of 11,300 cells/μL. Liver function tests were mildly elevated, as follows: lactate dehydrogenase, 294 U/L (normal, 88 to 196 U/L); serum aspartate aminotransferase, 298 U/L (normal, 5 to 35 U/L); and alkaline phosphatase, 246 U/L (normal, 16 to 95 U/L).

One week later, abdominal ultrasound was performed on an outpatient basis for further elucidation of right upper quadrant pain, and a large (7-cm × 9.5-cm × 8-cm) echogenic mass was noted superior to the right kidney. When the transducer was pressed against the patient's abdomen for better visualization of the mass, all of her previously reported symptoms were exacerbated. Her blood pressure rose precipitously to 250/150 mm Hg, and her electrocardiogram showed a sinus tachycardia with T- wave inversion in the inferior and anterolateral leads.

She was admitted to the cardiac intensive care unit with the presumed diagnosis of a pheochromocytoma. Blood pressure was rapidly and easily controlled with topical nitroglycerin paste and one sublingual 10 mg capsule of nifedipine; hypotension was avoided. With hydration, blood sugar fell from 586 mg/dL (32.5 mmol/L) on admission to 439 mg/dL (24.4 mmol/L), and subsequently to 290 mg/dL (16.1 mmol/L) over an 8-hour period. Similarly, bicarbonate fell from 23 to 17 mmol/L and then to 14 mmol/L. Blood gases obtained with the two latter values yielded pH values of 7.33 and 7.23. The diagnosis of diabetic ketoacidosis was confirmed with 4+ glucosuria, 4+ ketonuria, and a serum ketone level of 311 mg/dL (5.36 mmol/L). Serum lactic acid was 9 mg/dL (0.1 mmol/L).

A continuous intravenous (IV) insulin drip resolved the patient's ketonemia and ketonuria. The IV drip was then replaced by a subcutaneous insulin regimen guided by frequent glucose determinations. Blood sugar was maintained between 120 and 150 mg/dL (6.67 to 8.33 mmol/L) with 22 to 44 units of regular human recombinant crystalline zinc insulin per day. Islet cell antibodies were not evident. Widespread T-wave inversions persisted on the electrocardiogram, but the patient did not evolve a myocardial infarction.

The diagnosis of pheochromocytoma was pursued with a simultaneous intravenous contrast and Gastrografin (meglumine diatrizoate) swallow examination under CT, which confirmed the size of the mass and demonstrated no lymphadenopathy or local spread. There was no evidence of hepatic disease, metastasis, or contralateral adrenal mass. Urine and serum catecholamines were markedly elevated (*Table*).

Phenoxybenzamine therapy was initiated at 10 mg orally twice daily, and the dose was increased every other day until it reached 20 mg twice daily. This therapy controlled the patient's blood pressure, but she developed orthostatic symptoms, and the dose was decreased to 20 mg in the morning and 10 mg in the evening. After ketoacidosis resolved, and in the week

prior to surgery, she required 11 L of normal saline to correct hypovolemia. She received 2 units of packed red blood cells in preparation for surgery after her hematocrit level dropped from 40% to 29%. Tachycardia at rates of 130 bpm developed on phenoxybenzamine, and propranolol was added to the medical regimen. The last dose of phenoxybenzamine was withheld prior to surgery, and prophylactic steroid coverage was started.

During surgery, IV fluid and nitroprusside were used to compensate for wide shifts in blood pressure. A vascular tumor was found overlying the right renal vasculature and pushing the kidney downward. The left adrenal appeared normal, as did the remainder of the abdomen. No metastases were identified. The right adrenal was removed; the operation was uncomplicated. A 222-g well-circumscribed mass occupied the bulk of the excised adrenal, with histopathological findings classic for a pheochromocytoma.

The postoperative course was unremarkable, and the patient's symptoms and electrocardiographic changes resolved immediately after the procedure. At 19 months after surgery, the patient is well and taking no medications. Her blood pressure is 120/70 and blood sugar estimations average 90 mg/dL (5 mmol/L). An oral glucose tolerance test performed 7 months postoperatively was normal: at baseline, glucose was 84 mg/dL; 30 minutes after challenge this value rose to 127 mg/dL and returned to 79 mg/dL at 60 minutes. Over the next 2 hours, serum glucose remained between 78 and 103 mg/dL. Glycosylated hemoglobin (HbA1c) was 5% (normal, 0.15 to 8.8 %) and plasma and urinary catecholamines remained in the normal range (*Table*).

DISCUSSION

The unusual feature of the otherwise classical presentation for pheochromocytoma in this woman was the development of diabetic ketoacidosis. Mild glucose intolerance with elevated blood sugar has been noted in numerous cases of pheochromocytoma dating back to 1912,[1] yet diabetic ketoacidosis has not been previously described. Most often, paroxysmal hyperglycemia was associated with paroxysmal hypertension, though the degree of one was not indicative of the degree of the other.[2] In a study of 77 patients with pheochromocytoma, hyperglycemia was present in 66% of patients with persistent hypertension and in 56% of those with paroxysms.[4] Return of carbohydrate balance with surgical excision of the tumor has been noted from the first reports of successful surgery in these cases.[5] As a rule, glucose tolerance is usually restored immediately,[2,6–8] although there may be relative insulin resistance in the early postoperative period.[3] In patients who continue to require treatment, the question of possible pre-existing diabetes mellitus has been raised.[9,10] Rarely, no improvement is seen; in such cases the possibility of true diabetes mellitus or multiple tumors[11] must be considered.

In patients with pheochromocytoma, glycosuria or ketonuria sufficient to require insulin therapy is rare,[11,12] and to the best of our knowledge diabetic ketoacidosis with pheochromocytoma has never been fully documented.

In 1944, Duncan[13] reported a case of a man who had glycosuria and an "elevated CO_2 combining power."

In 1949 DeVries, reviewing the 50 cases of pheochromocytoma which had been reported at that time, found that 24 patients had glucose intolerance, and 5 had frank diabetes mellitus. Following surgery, 3 of the 5 diabetic patients returned to normal glucose homeostasis.[2] He reported two cases of his own, and in one, "The metabolic disturbance was at times so severe that it constituted the principal feature of the disease. It was then accompanied by severe acidosis, very high blood sugar levels and [glycosuria]." However, he reported few specific laboratory values aside from blood and urine sugar levels and 4+ ketonuria. He felt that ketoacidosis could not occur in cases of pheochromocytoma because the depletion of hepatic glycogen which stimulates the production of ketone bodies in long-standing diabetes mellitus is not found with pheochromocytoma.

Excessive levels of catecholamines are known to have profound effects on carbohydrate metabolism. Their primary effect seems to stem from interference with pancreatic insulin secretion,[14] but other contributing factors include impaired glucose tolerance, stimulation of glycogenolysis in muscle and the liver, induction of lipolysis in the muscles with mobilization of free fatty acids, and stimulation of hepatic gluconeogenesis.[15,16] Furthermore, peripheral glucose utilization is inhibited,[17] leading to reduced glucose clearance from the circulation[18] and impaired gastrointestinal absorption of glucose.[19]

The pharmacology of glucose intolerance associated with catecholamine excess is intriguing. Increases in glucose delivery and decreases in glucose clearance are epinephrine-induced and are mediated mainly by beta-adrenergic mechanisms.[20] Increments in blood glucose and decrements in glucose clearance have been

reported with plasma epinephrine levels of 150 to 200 pg/mL.[21] These direct effects are augmented by concomitant indirect inhibition of insulin secretion mediated by alpha-2 receptors.[6,7,22–26] When epinephrine levels exceed 400 pg/mL,[21] the alpha-2 inhibitory effects are believed to predominate over the beta-2 stimulatory effects, and glucose intolerance is exacerbated.

In patients with pheochromocytoma, hyperglycemia is thought to enhance the re-esterification of free fatty acids. In the past, this phenomenon was invoked to explain why diabetic ketoacidosis was not observed in patients with pheochromocytoma.[3] At the same time, norepinephrine infusion in man results in an elevation of plasma ketone body concentration that may be attributed in part to a lipolytic effect and also to a separate ketogenic effect involving a combination of factors: (1) a direct effect of norepinephrine on hepatic metabolism; (2) simultaneous suppression of plasma insulin concentration and/or (3) elevation of plasma glucagon concentration[27]; (4) increased ketone body production from augmented free fatty acid supply to the liver; (5) accelerated hepatic ketogenesis; and (6) modestly decreased metabolic clearance of ketone bodies.[28] Acute insulin deficiency augments all of these effects and results in progressive ketosis. Therefore, it has become classic teaching that diabetic ketoacidosis rarely occurs in patients who do not have coincidental diabetes mellitus.

Given a clearer understanding of the mechanisms of glucose intolerance in patients with pheochromocytoma, what are the expected effects of pharmacologic agents prescribed preoperatively for patients with pheochromocytoma?

Alpha blockade has been associated with improved glucose tolerance in patients with pheochromocytoma[7,22,23] but has also been suggested as a potential source of acidosis in states of excessive catecholamine production.[27,29] This results from the reversal of those events that enhance re-esterification of free fatty acids to triglycerides. When hypotension was induced in dogs by means of controlled hemorrhage, catecholamine production increased, but systemic delivery of free fatty acids did not occur until alpha-adrenergic blockade was instituted. Thus, alpha blockers and other vasodilators might increase adipose flow and the release of free fatty acids into the circulation. However, this could not have contributed to the acidosis seen in our patient, since she was acidemic even before therapy was initiated.

There is not enough evidence to predict the effect of beta blockade on glucose tolerance in pheochromocytoma. Calcium-channel blockers are frequently used as first line agents for treatment of accelerated hypertension and have been suggested as useful agents in patients with pheochromocytoma.[30–32] While nifedipine-induced glucose intolerance[33–35] has been reported, its effect on glucose intolerance in patients with pheochromocytoma has not been discussed.

Our patient clearly had ketoacidosis without lactic acidosis. She had lost 10 lb in the month prior to her admission, and elevated blood sugar was noted 2 weeks prior to her ketoacidosis. During the episode of acidosis, her serum ketones were markedly elevated. Possible explanations for her ketoacidosis include high levels of epinephrine, other as yet unidentified products secreted by the tumor, or effects of pharmacologic therapy. The return of her blood sugar levels to normal immediately postoperatively seems to rule out a diabetic propensity, and seems to indicate that her ketoacidosis occurred in the setting of intact pancreatic function.

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