Medical Journal of the
Islamic Republic of Iran

Volume 11
Number 3
Fall 1376
November 1997

INSULIN REQUIRING DIABETES MELLITUS AS A FEATURE OF PHEOCHROMOCYTOMA: REPORT OF A CASE

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ABSTRACT

We report the case of a 65 year old man with recent onset of insulin requiring diabetes mellitus, frequent attacks of anginal chest pain, paroxysmal hypertension poorly controlled with three medications, hyperlipidemia, and mild renal insufficiency. The patient was found to have pheochromocytoma of the left adrenal gland, resection of which resulted in total resolution of diabetes, hypertension, chest pain, hyperlipidemia and renal failure, with no requirement for any further medical management.

Keywords: Pheochromocytoma, Diabetes mellitus, Hypertension

MJIRI, Vol. 11, No. 3, 255-258, 1997.

INTRODUCTION

Pheochromocytoma is an uncommon and insidious disease, manifesting with persistent or paroxysmal hypertension, and in some cases with normal blood pressure. Abnormalities in the metabolism of glucose and insulin are not uncommon in patients with pheochromocytoma. Due to the paucity of signs and symptoms in some patients, the occurrence of glucose intolerance and/or hyperglycemia in up to one-third of these patients, and the high incidence of hypertension complicating the course of diabetes, many patients with pheochromocytoma are not diagnosed pre-mortem. In one study, for each patient that was diagnosed antemortem, there were three cases that were diagnosed post-mortem.[1] We report a patient with recent onset of poorly controlled hypertension, diabetes mellitus, hyperlipidemia, mild renal insufficiency, and frequent bouts of anginal chest pain whose work-up revealed a 7×10 cm left suprarenal mass consisting of a benign pheochromocytoma, resection of which was followed by total resolution of all the associated conditions.

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Case report

The patient is a 65 year old male, a native resident of Tehran, with a two-year history of diabetes mellitus initially treated with glibenclamide 15 mg daily which, due to poor glucose control, had been changed to NPH insulin, 40 units daily administered subcutaneously. Despite insulin therapy, the patient experienced frequent episodes of hyperglycemia and his fasting blood glucose measurements were generally in the 200-300 mg/dL range, with no episode of diabetic ketoacidosis. The patient also had a history of hypertension for 3 years which had been noticed to be paroxysmal in nature and as high as 240/120 mmHg despite medical therapy. The patient suffered from

episodes of headaches, flushing, chest pain, palpitation, sweating, nausea, vomiting, and occasional fainting. The patient was receiving alpha-methyldopa 500 mg tid, nifedipine 10 mg qid, and propranolol 40 mg tid for blood pressure control, with poor response. He also complained of frequent episodes of chest pain requiring sublingual nitroglycerin despite taking propranolol and isosorbide dinitrate on a regular basis. Laboratory determinations were as follows: Serum Na^+, 140 mEq/L; K^+, 5.1 mEq/L; Cl^-, 106 mEq/L; HCO_3^-, 14 mEq/L; BUN, 40 mg/dL; Creatinine, 1.8 mg/dL; Triglycerides, 551 mg/dL; Cholesterol, 259 mg/dL. ECG and chest x-ray were normal. A 24 hour urine collection (830 mL) yielded a vanillylmandelic acid level of 13.6 mg (normal <11 mg in 24 hours).

With a clinical impression of pheochromocytoma, the patient received 5 mg of intravenous phentolamine which resulted in a decline in blood pressure from 230/120 to 170/100 mmHg. A computerized tomographic scan of the abdomen revealed a 7.0 cm mass in the left adrenal gland region without any evidence of metastasis to intra-abdominal or retroperitoneal organs. The patient underwent removal of the left adrenal mass while his blood pressure was controlled with intravenous infusion of nitroprusside and propranolol, as well as large quantities of normal saline and 900 mL blood. A 7 by 10 cm mass replacing the left adrenal gland was removed. The tumor was primarily from the adrenal medulla and consisted of pleomorphic large acidophilic cells separated by vascular channels and delicate fibrous tissue with a few cells containing brownish pigments. There was no evidence of abnormal mitotic activity or invasion of the capsule. The pathology was compatible with the diagnosis of benign pheochromocytoma of the left adrenal gland. After surgical removal of the tumor, the patient developed normal blood pressure (120-130/75-80 mmHg) with no need for antihypertensive medication. The patient was also found to have normal fasting blood glucose levels (100-110 mg/dL) not requiring any insulin or oral hypoglycemic agents, as well as normal serum triglyceride and cholesterol levels of 190 mg/dL and 197 mg/dL, respectively. The patient's BUN and serum creatinine levels were reduced to 20 mg/dL and 1.2 mg/dL, respectively. Furthermore, he did not develop any more episodes of chest pain and was taken off propranolol and isosorbide dinitrate treatments.

DISCUSSION

Pheochromocytoma is a tumor comprised of cells from neural crest origin. These tumors which secrete catecholamines, predominantly involve the adrenal medulla. However, they may also occur in sympathetic ganglia, carotid body, aortic chemoreceptor, bladder wall, and mediastinum, among other places. The true incidence of pheochromocytoma is not well known. In one study, 0.13% of autopsies of the general population had pheochromocytoma and it is estimated that less than 1% of patients with systemic hypertension are due to pheochromocytoma.[1] The three most important symptoms of pheochromocytoma are paroxysmal headache, excessive sweating, and palpitation with or without tachycardia. In a report on 76 patients with pheochromocytoma, 73 patients had one or more, and 55 patients had at least two of these symptoms.[2] In another report, the triad of palpitation, headache, and paroxysmal sweating in hypertensive patients had a sensitivity and specificity of 91% and 94%, respectively, and the absence of all three had an exclusion value of 99.9%.[3] Other symptoms occurring less frequently are pallor, anxiety, nervousness, tremor, nausea with or without vomiting, fatigue, and chest or abdominal pain. Although hypertension is the most common clinical finding in pheochromocytoma, it may not be uniformly present. In one study, of 54 autopsy-proven cases of pheochromocytoma, only 60% had been hypertensive, two-thirds with persistent and one-third with paroxysmal elevations in blood pressure.[1] Other findings include abdominal mass, postural hypotension (50-75%), weight loss, and metabolic disturbances, in particular hyperglycemia. In a report from Mayo Clinic on 76 patients with pheochromocytoma, 20-30% of the patients with paroxysmal or persistent hypertension had fasting hyperglycemia.[2] However, it was not mentioned if any of these patients had frank diabetes mellitus requiring insulin therapy. In a report on 58 patients from the United Kingdom, 16% had either diabetes, glycosuria, or an abnormal glucose tolerance test.[4] In that report, 2 of 9 patients had required insulin therapy. Furthermore, in a review of 60 patients with a diagnosis of pheochromocytoma, 24% were found to have glucose intolerance/diabetes mellitus as defined by fasting glucose levels>7.0 mmol/L (>126 mg/dL).[5] There are also several case reports of frank diabetes in association with pheochromocytoma; however, the course was complicated with ketoacidosis in only one case.[6-10] Glucose intolerance has been attributed to the excessive catecholamines suppressing insulin release, and inducing glycogenolysis and peripheral resistance to insulin action.[10,11] These could be reversed by pharmacological blockade of the alpha-adrenergic receptors, and remit with removal of the tumor.

The present case is another example of the association of overt clinical diabetes mellitus and pheochromocytoma. The use of a non-selective beta-blocker (propranolol) may have also contributed to the

development of hyperglycemia and abnormal lipid profile as reported before.[12] Our patient had frequent episodes of anginal chest pain which has been reported in 12% of patients[13] and may be due to catecholamine-induced coronary vasospasm. In the present case, resolution of hypertension, diabetes, hyperlipidemia, anginal chest pain, and mild renal insufficiency, after resection of the tumor, indicates that they were all secondary complications of pheochromocytoma rather than primary disorders.

The presence of pheochromocytoma was suspected in our patient on the basis of relevant clinical clues and was further supported by an abnormally elevated urinary vanillylmandelic acid (VMA) level, although the VMA test should have ideally been performed in the absence of drugs that interfere with its measurement, i.e., alpha-methyldopa and nifedipine. In light of laboratory tests available to confirm the diagnosis of pheochromocytoma, a plasma total catecholamine (norepinephrine+epinephrine) level of >950 pg/mL has a sensitivity and specificity of 88-100% and 93-100%, respectively.[13-15] A level of >2000 pg/mL has a specificity of 100% but a sensitivity of only ~70%.[14] A recent study has suggested that the increase in plasma concentration of metanephrines (metanephrine+ normetanephrine) is greater and more consistent than the total catecholamine level.[16] In that report, no patient with pheochromocytoma had a normal plasma concentration of metanephrines (MN+NMN). Moreover, this test had a sensitivity and negative predictive value of 100% which was superior to 85% and 95%, respectively, for plasma total catecholamines (E+NE).[16] Furthermore, they found similar rates of false-positive results (i.e., specificity) with both tests; 15% and 18% , respectively.[16] Other tests which have been used are urinary metanephrines (NM+NMN) of >1.8 mg/24 hours (sensitivity: 70-90%; specificity: 80-100%), urinary VMA level of >11 mg/24 hours (sensitivity, 30-60%; specificity, 98-100%).[13-15] There are also pharmacological diagnostic tests, both provocative (e.g., glucagon test) and suppressive (clonidine test), which are available to further assist the diagnosis when the clinical picture is suggestive of pheochromocytoma but the above-mentioned test results are equivocal.[13-15]

After the diagnosis is established, localization of the tumor becomes necessary both to confirm the diagnosis and to plan for surgical resection. Both CT scan and MRI have very high localizing precision. As a non-ionizing imaging technique,[17] MRI is the procedure of choice in pregnant women with no danger to the fetus. Scintigraphic localization with radio-iodinated ^{131}I-metaiodobenzylguanidine (MIBG) would provide both anatomic and functional characterization of the tumor.[18]

After diagnosis and localization, the treatment of choice is surgical resection of the tumor which is curative in most cases. Surgery without pre-operative preparation can lead to death. Therefore, medical management at least ten days prior to surgery is mandatory. Alpha-adrenergic blocking agents such as phenoxybenzamine, 20-100 mg qd, or prazosin are most commonly used. Calcium channel blockers have also been used effectively for both blood pressure control and cardiovascular complications such as coronary vasospasm. Hypertensive crisis is commonly managed with intravenous sodium nitroprusside, phentolamine, or nicardipine. Particular attention should be paid to postoperative hypotension which is due to volume contraction, withdrawal of catecholamines, and pre-operative use of alpha-adrenergic blocking agents. Aggressive volume replacement with normal saline and whole blood transfusion preoperatively and during surgery is of utmost importance. Postoperative hypoglycemia is another complication which may be due to excessive release of insulin after withdrawal of catecholamines. Persistent hypertension after surgery may indicate either residual or metastatic pheochromocytoma, hypertensive vasculopathy due to chronic severe hypertension, or merely a sign of pre-existing essential hypertension. For more details in the pathophysiology, diagnosis, and treatment of this disorder, we refer the reader to two recent excellent reviews on the subject.[19,20]

ACKNOWLEDGEMENT

The authors would like to thank Ms. Laura Furdek for her secretarial assistance in the preparation of this manuscript.

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