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A Case Report of Pheochromocytoma Managed at Federal Medical Centre, Owo. Ondo State, Nigeria

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Abstract: ***Background: Pheochromocytoma is a very rare tumour of the sympathetic nervous system. It accounts for less than 1 in 1000 cases of hypertension. Objectives: To emphasis the need for high index of suspicion and possibility of cure in patient with secondary hypertension like pheochromocytoma. Case Report: A 26 years old lady hypertensive was referred to our facility from Adekunle Ajasin University, Akungba Ondo state, Nigeria. She presented with 13 years history of recurrent headache, excessive sweating, tremor and palpitation. She has a positive family history of hypertension in both parents and also her elder sister. Examination revealed heart rate of 106beats /minute and blood pressure 160/110mmHg sitting and 150/100mmHg standing, JVP not elevated and heart sounds were S1 and S2 only. Other systems were essentially normal. Assessment of severe hypertension was made with suspicion of secondary hypertension most likely pheochromocytoma. Blood pressure was controlled with atenolol and prazocin. Diagnosis was confirmed by markedly elevated 24hours urinary norepinephrine and dopamine and catecholamines metabolites. Abdominal ultrasound and computerized tomography, magnetic resonance imaging all revealed right adrenal tumour. Patient had successful resection of right adrenal gland done and weaned from antihypertensive over 3months. She has been normotensive for 8years on follow up. Conclusion: A high index of clinical suspicion, an unrelenting effort at diagnosis through adequate investigations and prompt intervention are indispensable tools in successfully managing patients.***

Keywords: Hypertension and Pheochromocytoma

1. Introduction

Pheochromocytoma is a very rare tumour of the sympathetic nervous system. Endocrine causes of hypertension generally, account for less than 5% of all cases of hypertension, and of all these, pheochromocytoma accounts for less than 1 in 1000 cases of hypertension. Herein, we present a case of 26year old lady who presented to us with 13years history of recurrent headache, excessive sweating, tremor and palpitation with family history in both parent and elder sister to emphasis the need for high index of suspicion among healthcare giver of rare diseases.

2. Case Report

A 26 year old lady diagnosed hypertensive referred to our facility from Adekunle Ajasin University, Akungba. She presented with history of recurrent headache, excessive sweating, tremor and palpitation of 13years duration. She had 3 episodes of hypertensive crises prior to presentation and positive family history of hypertension in both parents and also her elder sister. The review of other systems was not contributory. She had used different anti hypertensive prior to presentation mostly amlodipine and propranolol and was on atenolol at the time of presentation but with poor blood pressure control, hence her referral for specialist care from her university health centre.

Examination revealed a young lady, conscious but restless, not pale, anicteric, not cyanosed, no asterixis, dehydrated but no pedal oedema. She had a pulse rate of 106 beats per minute which was regular and of normal volume. The blood pressure was 160/110mmHg (sitting) and150/100mmHg (standing). 1st and 2nd heart sounds only. She had respiratory rate of 20cycles per minute and the lung bases were clear. Other systems were essentially normal.

An assessment of severe hypertension was made to keep in view secondary hypertension most likely pheochromocytoma. Patient was admitted for 48 hours at Emergency unit. Investigations were ordered and she was placed on atenolol 100mg daily and prazocin 2mg twice daily for blood pressure control and rehydrated with intravenous fluid.

Investigations results include; fasting blood sugar and 2 hour post prandial were within normal limits. Total cholesterol, LDL, and HDL were within normal ranges but Triglyceride was low, 0.3mmol/l (normal 0.45-1.72mmol). There was hypochloremia, 84mmol/l (Normal 94-110) and hypocalcemia 1.2 mmol/l (2.25-2.75). Other electrolytes, phosphates, urea and creatinine were within normal limits. Urinalysis was normal. Full blood count with differentials revealed relative lymphocytosis of 68%, other blood cells were within normal ranges. Electrocardiography revealed heart rate of 100bpm, sinus rhythm and normal axis. Echocardiography revealed normal study. Electroencephalogram done for the patient was entirely normal.

Catecholamines

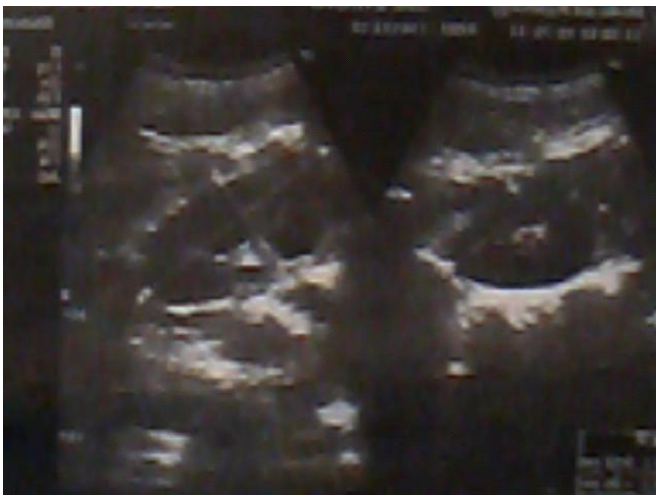
Test	Results	Reference
U-volume	1750ml/24hrs	600- 2400ml
U-creatinine	12.1mmol/24hrs	9.0 – 17.7
24hr epinephrine excretion	11mmol/24hrs	<109
Epinephrine/creatinine ratio	0.91	<12.34
24hrs Norepinephrine Excretion	3046mmol/24hrs	<473
24hr Dopamine excretion	4442nmol/24hr	<2612
Dopamine/Creatinine ratio	367.3	<184.5
Norepinephrine/Creatinine ratio	2519	<30.1

Catecholamines Metabolites

Test	Results	Reference
U-Normetanephrine	47430mmol/24hrs	
dU-Normetanephrine	83003mmol/24hrs	573-1932mmol/24hr
U-Normetanephrine/ creatinine ratio	5856	26-200
U-Metanephrine	192mmol/24hrs	
dU-Metanephrine	336mmol/24hrs	375-1506mmol/24hr
U-metanephrine/ creatinine ratio	24	5-90
U creatinine	8.1mmol/24hrs	

Urine catecholamine and its metabolites were markedly raised despite normal renal function.

Abdominal ultrasound scan revealed liver, gall bladder, pancreas, and spleen were normal in outline and echogenicity. Both kidneys were normal in site, size, outline and echotexture, with good corticomedullary differentiation. The pelvicalyceal systems were not dilated. The right adrenal gland was markedly enlarged with a homogenous echotexture which measured 6.3 x 4.16cm. No area of calcification was seen. The left adrenal gland was not visible. The urinary bladder, the uterus and both adnexae were normal.



Abdominal computeried tomography scan revealed both kidneys showed normal size and position. The renal parenchyma was normal in width and structure. The renal pelvis and calices showed normal configuration. The urinary drainage tract was unobstructed. The left adrenal gland was unremarkable. The tumour mass was seen in place of the right adrenal gland with heterodense structure. A single small calcification was seen in the upper lobe of the mass. There were evidences of some hyperdense zones-cysts; the biggest of these was 11x16mm. The common size of the tumour was in the axial plain 42x41mm and in sagittal view 57x47mm. The hepatobiliary system was normal though the portal vein, hepatic veins and the inferior vena cava appeared dilated. The spleen, pancreas, imaged portions of the lung, and the urinary bladder were normal. No evidence of lymphadenopathy. The uterus appeared normal. A right ovarian cyst measuring 29x23mm was seen.

Magnetic resonance imaging revealed well-defined soft tissue signal intensity with right suprarenal mass lesion showing multiple cystic areas. The left adrenal gland showed normal morphology and signal intensity. No other significant abnormality detected.

The blood pressure was well controlled following 6weeks of medications 110/70mmHg on outpatient follow up.

Patient later had surgical resection of the right adrenal mass.

Tumour was sent for histopathology and also for immunohistochemistry. Histopathology revealed a nodular mass, 5x5x4cm.

Cut section was well circumscribed with areas of haemorrhage. Sections showed normal adrenal cortex along with tumour. The tumour comprised of nests of cells with vesicular nucleus and vacuolated oesinophilic cytoplasm. The nuclei were pleiomorphic with many bizzare forms. There were areas of haemorrhage. Capsular and vascular invasion not seen. Immunohistochemistry revealed cells which expressed chromogranin and synaptophysin. Negative for cytokeratin.

Final diagnosis was that of pheochromocytoma (benign).

Post-operative measurement of 24 hour urine levels of metanephrine and vanillymandelic acid (VMA) 3weeks post surgery revealed;

Metabolite	level	Reference
Metanephrine	120ug	25-312ug/24hrs
VMA	3.9ug	0.0-13.6ug/24hrs

Patient became normotensive following surgery and she was gradually weaned off antihypertensive over 3 months. She was on clinic follow up for 1 year and later on phone call follow up for 8years with normal blood pressure without antihypertensive.

3. Discussion

Pheochromocytoma is a very rare tumour of the chromaffin cells of the adrenal gland. It occurs in approximately 0.1% of the hypertensive population. It is an important treatable cause of hypertension but may be fatal if not promptly diagnosed and properly treated. It typically presents with features of cardiovascular instability with symptoms which may be intermittent or

constant depending on whether the catecholamines are released continuously or in paroxysms. Patients usually present with anxiety or panic attacks, palpitations, tremor, sweating, headache, flushing, nausea, vomiting, weight loss, constipation, or diarrhea and tachycardia. It should also be suspected in patients with aberrant reactions to medications like opioids and tricyclic antidepressants. Also in patients with unexplained hypotension or shock in association with surgery or trauma because of blunted sympathetic reflexes and reduce plasma volume. These features are due to catecholamine excess. This patient had 3 episodes of hypertensive crises prior to presentation. This is a common feature in patients with pheochromocytoma with progressive increase in the frequency of occurrence. This could be precipitated by emotional distress or anxiety, anesthesia, physical activities that could compress the tumour e.g. postural changes, exercise, pregnancy, weight lifting and urination. Also the use of some drugs could precipitate hypertensive crises in patients with pheochromocytoma such as; opiates, histamine, adrenocorticotropin, saralasin, and glucagon. These agents appear to release catecholamines directly from the tumour.

Others includes monoamine oxidase inhibitors e.g. phenelzine, decongestants, amphetamines, cocaine, foods rich in tyramine e.g. some wines, processed meats or fish, bananas, over-ripe food etc.

Pheochromocytoma may be inherited as an autosomal dominant trait in about 25% of patients. In such patients there may be a family history of the disease or 'just' hypertension. However there may be a history suggestive of other coexisting diseases. Examples of this syndromic presentation are seen in association with multiple endocrine neopasia type II (MENIIA & MENIIB), Von Hippel Lindau disease, neurofibromatosis I and familial paraganglioma. Pheochromocytoma may also be accidentally detected while investigating for these other conditions. Features suggestive of familial cause include bilaterality, multicentricity and age of onset less than 30 years. However, patients with solitary adrenal pheochromocytoma, negative family history, and no evidence of associated disease may still have an inherited form of the disease. This could be found with mutations of the succinate dehydrogenase subunit B and D (SDHB and SDHD) genes. This patient has a positive family history of hypertension in both parents and an elder sister. Also, the age of onset of this disease in the patient was about 13 years. All these are in favour of a possible familial cause in our patient. Thus, screening of the family members is indicated, for which she was properly counseled. However, family screening was not carried on account of financial difficulty.

Confirming the diagnosis of pheochromocytoma entails both biochemical and radiological methods. Ideally, the formal before the latter. Plasma levels of free epinephrine, norepinephrine and normetanephrine, metanephrine can be assessed but 24hours urinary levels of fractionated catecholamines and its metabolites were used in this patient. Also, clonidine suppression test may also be used to confirm diagnosis. This drug reduces plasma catecholamine in normal subjects and in patients with essential hypertension. This is not available in our facility.

The samples are best collected when the patient is symptomatic, in patients with episodic/paroxysmal presentations. The patient had markedly elevated urine levels of norepinephrine, dopamine and its metabolites. These levels were determined using high pressure liquid chromatography. However, patients on certain medications may have falsely elevated levels. Examples of such drugs are tricyclic antidepressants, beta blockers, amphetamines, dobutamine, isoprenaline, ethanol, phenothiazines, nitroglycerine, ephedrine, salbutamol, L-Dopa, monoamine oxidase inhibitors (MAOIs) and sodium nitroprusside. These tests should be done after withdrawal of the drugs for at least 5 days. The use of diuretics and hypovolemia may also affect the results. Our patient test was done 5 days after discontinuation of atenolol.

Intraadrenal tumours are localized with abdominal ultrasound, computed tomographic scanning or Magnetic Resonant Imaging. These show the site, size, unilateral or multicentrallity of the tumour.

However, extraadrenal tumours e.g. within the chest or bladder can be localized with chest Xray, computerized tomographic (CT) scan, magnetic resonance imaging (MRI), or Positron emission tomography scanning with 18F-dopa. Tumour that cannot be localized with standard imaging, a radionuclide scintiscan after administration of 123I Metaiodobenzyl Guanidine (MIBG) will localize functional catecholamine rich tissues by amine uptake process to produce external scintigraphic image. Abdominal ultrasound, computerized tomography and magnetic resonance imaging were done for our patient who localized the tumour at the right adrenal gland.

Fine needle aspiration of the tumour is contraindicated. This could provoke a fatal hypertensive crisis and severe hemorrhage.

Differential diagnoses like anxiety or panic attacks, alcoholism or alcohol withdrawal, use of sympathomimetic drugs e.g. cocaine, epinephrine, terbutaline, phenylpropanolamine, MAOIs, tyramine-containing foods, hyperthyroidism, menopause, hypoglycemia and abrupt discontinuation of short acting sympathetic antagonists e.g. clonidine, intracranial lesions especially posterior fossa tumours or subarachnoid hemorrhage may cause hypertension and increase excretion of catecholamines and their metabolites. These were rule out with imaging results confirming right adrenal tumour. Also, diencephalic/autonomic epilepsy may be associated with paroxysmal spells, hypertension, and increased plasma catecholamine levels. However, this is associated with aura, seizure or abnormal electroencephalogram.

The treatment of choice for pheochromocytoma is surgery. Preoperatively, patients are treated with alpha adrenergic blocker, Phenoxybenzamine and beta adrenergic blocker atenolol to avoid stress induced catecholamines excess and hypertensive crisis during surgery. Oral Prazosin and

intravenous Phentolamine are useful in treating paroxysms and as antihypertensives in patients being worked up for surgery. Other drugs useful in treating hypertension in these patients include calcium channel blockers, angiotensin converting enzyme inhibitors, and nitroprusside which is also useful in the treatment of pressor crises. Beta adrenergic blockage is achieved with the use of propranolol, atenolol or others. This should be introduced after alpha blockade to prevent paradoxic hypertension due to antagonism of B-mediated vasodilatation in skeletal muscle and unopposed action of alpha agonists resulting in peripheral vasoconstriction and exacerbation of the patient's hypertension.

The tumour may be resected laparoscopically by experienced hands. Surgical mortality is 2-3%. After surgery, catecholamine excretion returns to normal in about two weeks. Our patient was only able to do 24 hours excretion of metanephrine and VMA once due to financial difficulty 6months after surgeries which were within normal values. Patients with unresectable tumours due to metastasis or local invasion, or intercurrent illness that precludes surgery, treatment is medical with long term use of adrenergic blocking agents. This may require the coadministration of Metyrosine, an inhibitor of the enzyme tyrosine hydroxylase.

It reduces the production of catecholamines by the tumour. Recurrence, usually in the retroperitoneum is usually managed with combination chemotherapy. 5year survival rate after surgery is about 95% with recurrence rate of 10%. Complete removal cures the hypertension in ¾ of patients as seen in our patient, remaining ¼, the persistence of hypertension may be due to an underlying essential hypertension or irreversible vascular damage induced by catecholamines. Postoperatively, catecholamine excretion should be assessed yearly in asymptomatic patients and at the appearance of suggestive symptoms. Patient should be advised on annual lifelong plasma catecholamines and urinary VMA assessment, CT or MRI and periodic imaging with radio labeled MIBG to monitor for recurrence or metastasis. Also, patient should be counseled on annual cardiac evaluation, retinal examination and screening of family members.

4. Conclusion

A high index of clinical suspicion, an unrelenting effort at diagnosis through adequate investigations and prompt intervention are indispensable tools in successfully managing patients with pheochromocytoma or any other secondary cause of hypertension. This not only takes care of the hypertension which could be otherwise fatal, it also remove the economic burden from the cost of antihypertensive drugs, improves the patients quality of life and reduces the patient load in the ever busy hypertension clinic.

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