Pheochromocytoma: A Case Report and Review of Literature.

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SUMMARY :

The case history of a 13 years old boy with severe systemic hypertension is presented. The clinical suspicion of pheochromocytoma was confirmed on subsequent non-invasive and invasive workup. The patient underwent successful surgical removal of his tumor. As there is but passing mention and only one brief abstract of a documented case of Pheochromocytoma in the Pakistan medical literature, the details of this boy's history, workup and review of this condition is presented to increase awareness of the existence of this curable disorder in Pakistan.

Introduction :

Pheochromocytoma is a tumour arising from the neural crest tissue and mostly situated in the adrenal medulla (1). It is a rare disorder and accounts for < 0.1% of all cases with systemic arterial hypertension. While hypertension is a common problem in both the adult and pediatric age groups in Pakistan (2), local physicians appear not to be aggressive in the workup of secondary causes of hypertension. This view is supported by the fact that pheochromocytoma is cited only in passing in one paper (3) and a case history is mentioned in a brief abstract form (4) in our search of the Pakistan medical literature. We therefore report in detail the presentation, diagnostic workup and management of our case to attract attention of our physicians to the existence of this well known and treatable cause of secondary hypertension.

Case History :

A thirteen years old boy was referred from Abbotabad for the management of severe hypertension. He was admitted in the south ward of National Institute of Cardiovascular Diseases for workup and management of his hypertension.

He was alright one year back when he started complaining of headaches associated with vertigo. The headaches used to occur in the morning, were throbbing in character, all over the head and lasted 3 to 4 hours. For the last six months there was associated vomiting and sweating during the episodes of headache followed by palpitation and weakness lasting 15 to 30 minutes. Occasionally, he would get blurring of vision lasting 10 to 15 minutes but he never fell down nor lost consciousness.

He had been admitted to a hospital in Abbotabad (no records available) with this history and was found to have a very high blood pressure. He was given Tab. Methyldopa 500 mg TID, Tab. Propranolol 40 mg TID and a Thiazide + Triamterene combination diuretic OD. However his B.P. could not be controlled and he was referred to this Institute.

There was no past history of asthma, heart disease, tuberculosis, mumps, chicken pox, scarlet fever, small pox, infantile paralysis, typhoid, pneumonia, boils, siezures, nephritis injuries or surgical procedures. He had had measles and jaundice once each in early childhood and had had tonsillitis, "Malaria" and dysentry three to four times.

There was no family history of Ischemic

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Heart Disease, Diabetes, Hypertension T.B., Siezures, Psychiatric illness, Cancer, Rheumatism or Endocrinopathy.

Physical Examination :

The temp. was 37°C, Respirations 20 per minute, Pulse was 140 per minute (resting) and the supine B.P. in all limbs 220/140 m.m. Hg on admission.

The patient was a well-behaved, co-operative and intelligent young boy. Height was 56" and his weight was 65 lbs. There was pallor of the skin and no rash. Pupils were dilated but equal and reactive. Both the fundi showed Retinitis Pigmentosa with normal disc. Head and neck were normal. J.V.P. was normal. There was no Lymphadenopathy and the thyroid was not enlarged. Examination of the ears, nose, and throat revealed no abnormal findings.

Cardiovascular examination showed a radial pulse rate of 140/min, regular, normal volume and non palpable arterial wall. All peripheral pulses were equally palapable and there was no radio-femoral delay. The B.P. was 220/140 m.m. Hg. supine and 150/120 m.m. Hg. standing in both arms and 220/120 in both legs supine. The J.V.P. was normal.

Precordium was normal with apex beat visible and palpable in 5th left interspace just inside the mid clavicular line and was hyperdynamic. No thrill was palpable. S1 was normal and S2 was normally split. No. S3, S4, any murmur or pericardial rub was heard. Thoracic cage examination showed symmetrical expansion of chest with respiration, vocal fremitus and vocal resonance were equal on both sides. Percussion note was normally and equally resonant on both sides. Breath sounds were normal vesicular with no rhonchi or crepitations.

The abdomen was normal on inspection with no tenderness, spasm or guarding on palpation. Liver, spleen and kidneys were not palpable. There was no fluid thrill or shifting dullness. Gut sounds were normal. NO BRUIT PRESENT. Secondary sex characters and genitalia were normal for age. Rectal examination was negative.

Examination of the musculo-skelletal and neurologic system examination was negative.

Routine Laboratory examination :

Urine examination showed 2—3 W.B.C. per high power field. Repeat urine exam also showed traces of albumin. Haemoglobin was 11.4 G./dl., total white cell count was 7,400/c.mm., with 70% Polys, 27% Lymphos, 2% Monos and 1% Eos. The ESR was 52 mm in the 1st hour (Westergreen method). The random blood glucose was 117 mg./dl., Urea 20 mg/dl, Sodium 132 mEq/L and Potassium was 3.0 mEq/L. Serum enzymes were normal.

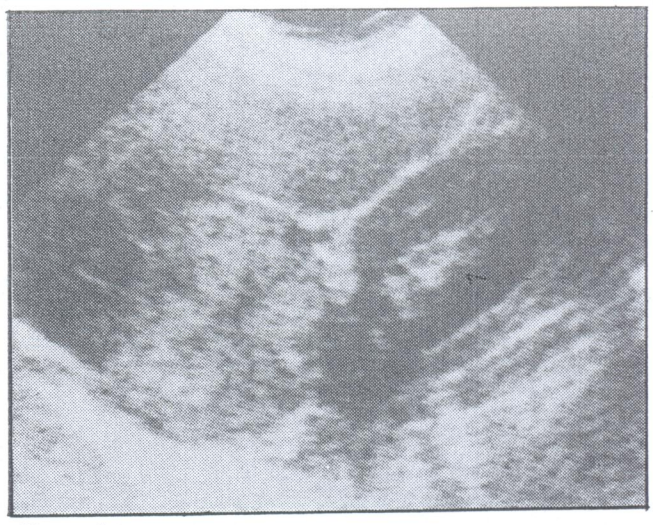

Figure 1 :

Ultrasonogram of the abdomen showing a large solid right suprarenal mass.

Plain X-Ray chest showed a heart size with prominence of the ascending and arch of aorta and normal lung fields and pulmonary vascular pattern.

The E.C.G. showed left ventricular hypertrophy by voltage criteria but no ST or T change. Investigations: A 24 hour urinary estimation was done and reported as 20 mg. (normal range 0.6 — 7 ng). Rogitine test was done with 5 mg. I/V phentolamine and a systolic B.P. drop of 50 mg Hg. and 55 mm Hg. diastolic BP was noted (more than 35 m.m. Hg is taken as confirmatory). Non-invasive localization of the pheochromocytoma was done by an abdominal ultrasound (Fig. 1) which suggested a large right suprarenal mass. Finally, an abdominal aortogram and selective right renal artery angiogram was done both to confirm the location and size of the tumor but more importantly to delineate the vascular supply of the tumor for the benefit of the surgeon in helping plan clamping venous and arterial connections (venous clamping is done before arterial clamping if possible). An unequivocal, very vascular right suprarenal tumour was

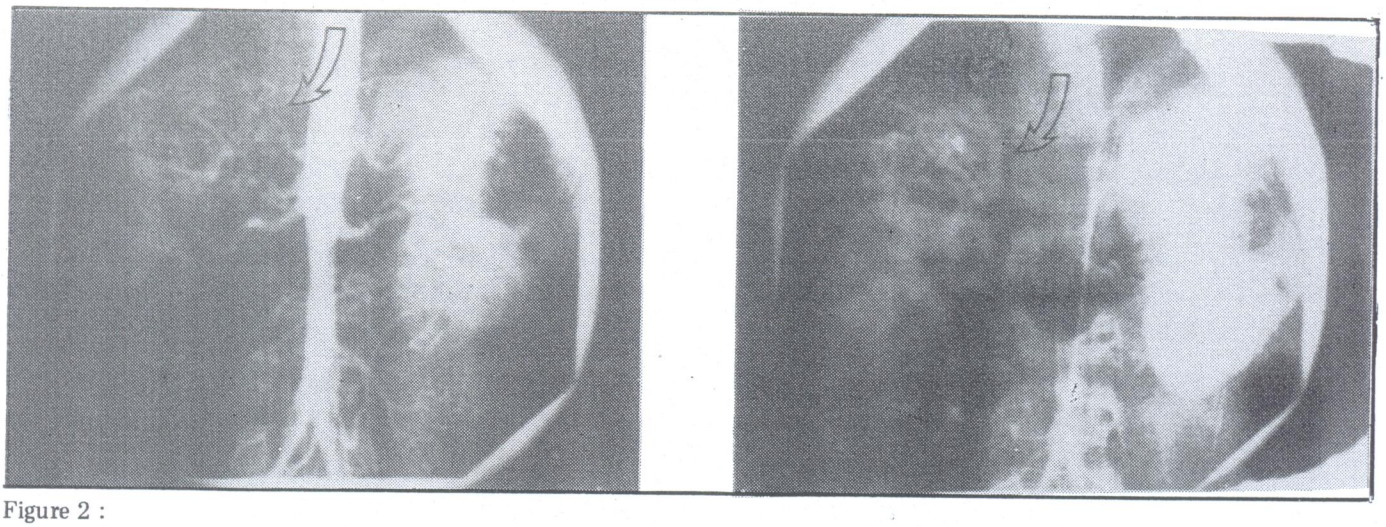

Figure 2 :

A&B Abdominal Aortogram. Arterial phase (A) shows the separate artery (arrow) to the right suprarenal area. Tissue (capillary) phase (B) shows the large ball-like right suprarenal very vascular tumour (arrow) i.e. the pheochromocytoma.

confirmed (Fig. 2 A&B)

Further Hospital Course :

The patient's old medications had been stopped as soon as the diagnosis of Pheochromocytoma was entertained and before specialized laboratory investigations were done. As phenoxybenzamine is not available locally, we chose labetolol 100 mg BID for its known action of both alpha and beta blockade. Volume repletion was slowly done along with B.P. control. Surgery was done by a usual approach to the right kidney and a large tumor mass of tennis ball size was removed. Post-operative course was uneventful. Pathological examination confirmed the tumour to be a pheochromocytoma.

Discussion :

This 13 years old young boy was well until about 1 year prior to admission when a variety of symptoms developed, and he was found to be suffering a very high blood pressure. This history of hypertension in this young boy made it mandatory to look for pheochromocytoma, coarctation of aorta, renovascular hypertension, primary aldosteronism, congenital adrenal hyperplasia and Wilm's tumor, neuroblastoma, severe and recurrent urinary tract infection and especially other parenchymal renal disease, polimyelitis, lead or mercury poisoning and obesity. This boy had most of the symptoms commonly reported in patients with Pheocnromocytoma. In a study from the Mayo clinic, Gifford et. al. (5) found that headache, increased sweating and palpitation occured in over 70% of patients with this disease and more than 30% of patients experienced chest pain, weakness, nausea and vomiting. Our patient also had severe orthostatic hypotension which is due to decreased plasma volume in these patients (6). The skin pallor is usually the result of intense vasoconstriction due high blood levels of circulating catecholamines. Our cases was also mildly anemic most likely due to past history of dysentry and poor diet due to poverty. Besides the anemia, all routine laboratory tests were normal except for the potassium which was 3.0 meg/L which can be explained by the fact that the patient was taking diuretics without potassium supplementation. The prominence of the ascending and arch of aorta on X-Ray chest was due to the severe hypertension.

The 24 hour urinary VMA was raised at 20 mg/24 hours (normal range 0.6—7 ng). It must be noted that the patient was off methyldopa and vanilla containing foods for 3 days prior to the collecting of urinary sample for VMA. The raised urinary VMA value was consistent with the clinical diagnosis of Pheochromocytoma and supported by the ultrasound of the abdomen which documented a large mass above the right kidney. Rogitine test was strongly positive with a B.P. fall of 55 m.m. Hg and an abdominal aortogram confirmed a large right supra-renal mass.

Clinical Characteristics of Pheochromocytomas :

Pheochromocytoma is usually a tumour of the adernal gland and is situated unilaterally in 90% cases with a right sided preponderance (1). It usually involves the adrenal medulla and can be found along the entire sympathetic ganglion chain particularly in the abdomen but also rarely in the thorax, neck and even in the wall of the urinary bladdar where they produce in unusual syndrome of paroxysmal attacks associated with micturition (7). Approximately 10% of Pheochromocytomas are familial, 10% bilateral, 10% occur in children and about 10% of these are malignant. The tumour is usually small and encapsulated but occasionally may weigh upto several pounds. In the famlial group there is an increased indidence of Von Recklinghausen's neurofibromatosis. Sometimes it occurs as part of multiple endocrine neoplastic (MEN) syndrome typically the MEN type—2 which is a triad of Pheochromocytoma, medullary carcinoma of thyroid gland and hyper-parathyroidism (8). In some patients the syndrome is associated with epidermal neuromas and skeletal defects.

The normal medulla contains about 80% of l-adrenaline and 20% of its precursor l-noradrenaline but the Pheochromocytoma secretes much larger amounts of noradrenaline than adrenaline as a rule, very rarely the reverse is true. In extra-adrenal tumours usually nor-adrenaline is the only catecholamine found. The catecholamines produce hyperglycemia and an increase in plamsa free fatty acids (1). The clinical features are due to the release of a mixture of both catecholamines.

Its highest incidence is in childhood and there is a second peak between the ages of 30 — 50 years. Either sex is affected (1). Usually no tumour is palpable abdominally but in about one third a mass may be felt. Many patients do not present with clear-cut attacks and the commonest mode of presentation is chronic hypertension, usually benign but rarely malignant. But when present the attack of hypertension with associated vasomotor phenomena last for about a quarter of an hour but some are of very short duration lasting a few seconds and others may last for hours or several days at a time (1).

Recently some insight into the complex physiologic manifestation of Pheochromocytoma has been forth-coming. There is no close correlation between catecholamine levels, including norepinephrine levels, and the arterial blood pressure. This finding may be due to states of the patient's volume, secretion of opposing vasodilator substances, particularly prostaglandin and most importantly in postsynaptic adrenergic receptor function. Adrenergic agonists directly affect receptor function through a process of desensitization, characterized by an uncoupling of the receptor from its effector mechanism for example adenatyl cyclase (9, 10). Later there is loss of receptors from the cell surface. After removal of agonists a rebound increase in both the function and the number of these receptors occurs. Thus a pheochromocytoma, which cyclically releases its cathcholamine stores, might produce different effects depending on the level of receptor function. It might be expected that a moderation of physiologic effects would occur after a prolonged period of catecholamine due to receptor function desensitization. In contract, when low catecholamine levels prodominate, receptors might increase in number and in the efficiency of their coupling — effector mechannisms. If a sudden release of cathecholamines then occurs, a striking physiologic response would be expected, the so called paroxysmal attacks associated with Pheochromocytomas. This event might be likened, almost in a mirror-image fashion to the rebound phenomenon described as the propranolol withdrawal syndrome.

Diagnosis :

Pheochoromocytoma might be categorised as the clinical entity with the greatest number of laboratory tests yet reported for its diagnosis. These tests can be divided into those that measure catecholamine levels or their metabolites (11) and those that evoke a pharmacologic effect (12, 13), the later can be subdivided into those that stimulate a hypertensive respone in patients with paroxysmal hypertension and those that produce a fall in blood pressure in patients with sustained hypertension. It should be noted that approximately 50% of patients with Pheochromocytoma have sustained hypertension.

The most commonly employed laboratory tests measure catecholamine metabolites in 24 — hours collections of urine. These metabolites incude vanilylmandelic Acid (VMA), metanephrine and normetonephrine taken together. Measurements of VMA and metanephrine detect over 95% of patients with a Pheochromocytoma.

Investigations at the Cleveland clinic (14) have suggested that the measurement of plasma catecholamines is more sensitive and more accurate. This assay is more difficult to perform and greater care must be taken to avoid artifactual increases in the catecholamine level for example even during venipuncture.

A recently reported biochemical assay is based on the finding that platelets actively concentrate catecholamines and thus an increased platelet catecholamine level appears to be a sensitive and reliable indicator of a Pheochromocytoma (15). With the availability of specific and accurate biochemical tests for confirming the diagnosis of Pheochromocytoma, provocative testing by using histamine, tyramine or glucogon which raise the B.P. is unreliable and also seems unreasonable in view of the potential dangers associated with such maneuvers. However, clonidine suppression test has been shown to be a reasonably safe and accurate method of confirming this diagnosis (16). This test employes clonidine, an alpha-2 partial agonist, that inhibits the release of catecholamines from synapses and generally decreases plasma catecholamine levels. Such an effect does not occur in patients with an autonomously functioning Pheochromocytoma.

Another test which involves the use of alpha adrenergic blocking drug phentolamine has been used but it can give false positive results and may induce dangerous hypotension. In this test 5 mg of phentolamine is injected rapidly in to a peripheral vein after maintaining an I/V line with 5% D/W and the B.P. is recorded prior to the injection and then every 30 seconds for first 3 minutes and then every minute for the following 7 minutes. An immediate drop in systolic B.P. of more than 35 m.m. Hg. or diastolic B.P. of more than 25 mm Hg. is a positive response. The systolic B.P. drop of 50 m.m. Hg. and diastolic B.P. drop of 55 mm Hg. in our patient was highly significant.

The most reliable method of diagnosis is the demonstration of increased secretion and excretion of catecholamines or their urinary metabolites including vanilylmandelic acid (VMA) and the meta-nephrines or meta-adrenaline and meta-nordrenaline (17). The plasma nonadrenaline may also be measured but is of less diagnostic value. The estimation of urinary VMA is the simplest and most convenient screening test and is the initial step in the workup. Its normal value ranges from 0.6 – 6.5 mg/24 hour. A confident diagnosis of Pheochromocytoma can usually be made from a 24 hour urine specimen provided the patient remains hypertensive during the urine collection. However, in myocardial infarction, severe muscular exertion, ingestion of bananas and vanilla containing foods and treatment with adrenaline or noradrenaline, the urinary VMA may be very high. Fluovometric estimation of catecholamines may be interfered with by alpha methyldopa and clonidine which the patient may be taking for hypertension or phenothiazine, tetracyclines, some vitamins, renal failure and jaundice. Monoamine oxidase inhibitors cause a greatly decreased excretion of VMA and so do the barbiturates and salicylates. VMA may be raised in some patients with neural crest tumours. If Pisano's method is used for measurement of urinary metanephrines, dietary and drug interference occurs very rarely (18).

Estimation of urinary metanephrines in a single voided specimen is diagnostically reliable but it is better to have a 24 to 40 hour sample examined. The upper limit of normal is 1400 micrograms 24 hour. It has been claimed that this test may be positive when the urinary VMA is negative but the reverse is rarely true. A falsely high reading may be obtained if the patient is taking chlorpromazine (17). Urinary catecholamines are commonly grossly elevated, the upper limit of normal being 100 micrograms per 24 hour.

Estimation of the plasma noradrenaline gives additional support to the diagnosis but is not essential, the range of supine resting plasma nor-adrenaline being 0.05 to 1.80 micrograms/L. The intermittent nature of catecholamine secretion by the tumour may result in normal plasma nor-adrenaline levels if measurements are made during a trough. It must be borne in mind that circulating nor-adrenaline may be increased during anxiety, left ventricular failure or following myocardial infarction.

Localization of the Tumour :

Some authorities say that it should be done at operation as over 80% of tumours occur in the adrenal and they are multiple in only 10% of cases (19). However an attempt must be made in our opinion to give the surgeon a pre-operative location but instructed to exclude other sites by close inspection at laparatomy.

Localization by Non Invasive methods :

Very rarely the tumour may be palpable. It was not palpable in our patient. Plain radiography and tomography may demonstrate a suprarenal mass which rarely may be calcified. I.V.P. may reveal distoration of the pelvis or displacement of the kidney in 30% of cases. The I.V.P. was normal in our case. C.T. scan is now-a-days becoming the most reasonable initial study to perform (17) but could not be carried out in our patient because the patient could not afford this test which is not yet available in government hospitals. Ultrasonic scanning is very helpful in localising these tumour. In our case a large, right sided supra-renal mass was detected on ultrasound.

Localization by Invasive Method :

Venous sampling from varous levels from the superior and inferior vena cavae and estimating the plasma noradrenaline content is helpful in diagnosing and localizing the tumour. Adrenal venography may prove of value for localising small adernal tumours and is indicated where other investigations have failed to reveal a tumour. Renal arteriography may be of value particularly as the tumour is vascular but carries risk of severe paroxysmal hypertension. This was done without problems in our patient who had been well prepared and hypertension controlled medically. Retroperitonal air insufflation is rarely done now-a-days and false positive results may occur. Recently a I^{125} derivative of benzyl guanidine has been used to localize these tumours by scintigraphic scanning. This agent, like guanidine, accummulates in adrenergic tissue via an active uptake mechanism (8, 20).

Treatment :

The treatment is surgical removal of the tumour. Medical treatment is aimed at preparing the patient for surgery or to control a hypertensive crisis by giving alpha adrenergic blocking drugs. Phentolamine, a non selective alpha antagonist has been a mainstay of the therapy. Nitroprusside also adquately controls the acute hypertension associated with this tumour (19). More prolonged effect can be obtained by the oral administration of phenoxybenzamine which covalently binds to alpha adrenergic receptors and blocks their activation for a prolonged period. Prazosin, a selective alpha-one antagonist is also effective in the treatment of hypertension associated with a pheochromocytoma (21). Beta blockade should never be undertaken without first obtaining adequate blood pressure control by alpha blockade, since such therapy may result in an unopposed alpha response with a paradoxical increase in the blood pressure and acute left ventricular failure. In additon to these measures these patients should have adequate volume repletion before any surgical procedure is undertaken because prolonged catecholamine exposure decreases extracellular fluid volume, and in particular, plasma volume. Our patient was initially sent to us on methyldopa, propranolol and a diuretic. When we started considering pheochromocytoma as the probable diagnosis we stopped both methyldopa (for VMA estimation) and propranolol and started him on labetalol 100 mg twice daily as phenoxybenzamine is not marketed in Pakistan. Penentolamine and nitroprusside are very short acting and since he already had severe orthostatic hypotension so prazosin was avoided. As expected, he responded reasonably well to the combined alpha-beta blockade of labetalol during the aortography and later at surgery no serious problems such as hypertensive crises occurred. No postoperative hypotension, shock or hypovolemia were encountered due to adequate fluid replacement before and during surgery.

After the surgery patient's recovery was uneventful, his pallor is gone and he has become pink. His blood pressure is maintained at 110/80 m.m. Hg. though with resting tachycardia for which a small dose of propranolol (10 mg TID) maintains pulse rate about 90 beats / minute. We expect this resting tachycardia to slowly disappear and all medication stopped in a few weeks time.

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