Endocrine Hypertension - Optimal Evaluation and Management

Sunil Ambulkar[1], Parimal Tayde[2], Mukund Ganeriwal[3], Makrand Randive[4]

ABSTRACT

Hypertension is a commonly encountered clinical problem all over the world. Since secondary hypertension is a potentially curable entity, it's timely recognition and optimal management is of utmost importance for the treating physician. Major causes of "Endocrine Hypertension" include Primary aldosteronism, Pheochromocytoma and Cushing's syndrome and other causes. Recent advances in biochemistry, immunoassays and imaging techniques have led to significant advancement in our understanding of these seemingly complex conditions. This review will focus on optimal evaluation and management of common causes of endocrine hypertension.

Key Words : Endocrine hypertension, Cushing's syndrome, Pheochromocytoma, Primary aldosteronism, Secondary hypertension

Introduction :

Hypertension is defined as a blood pressure more than 140/90 mm Hg recorded on 2 or more office visits for adults.

In 90 % of the cases, hypertension is primary, also called essential hypertension. The term "Secondary hypertension" is reserved for hypertension with identifiable cause. In around 10 % of the cases there is an identifiable cause[1]. Endocrine disorders as a cause of secondary hypertension comprise 5% - 10% of all patients with hypertension[1]. Although secondary hypertension and endocrine hypertension are rare entities, they are potentially curable with appropriate medical or surgical management. Common & as well uncommon conditions leading to hypertension are listed in ***Table 1.***

Table 1 : Causes of Secondary Hypertension

Cause	Clinical Features
Renoparenchymal Hypertension : GN & PCKD	H.T., Hematurea, Edema, Flank Pain, Renal mass
Renovascular Hypertension : Renal Artery Stenosis Fibromuscular Dysplasia	Renal Bruit
Endocrine Hypertension	
Primary hyperaldosteronism	Diastolic hypertension, muscle weakness, hypokalemia , metabolic alkalosis
Cushing's syndrome	Stria, weight gain, mooning of face, proximal myopathy, plethora, hirsutism, buffalo hump, central obesity
Pheochromocytoma	Headache, palpitation, sweating, pallor

[1]Associate Professor and HOD,
[2]Assistant Professor, [4]Senior Resident,
Dept. of Endocrinology, GMC and SSH Nagpur.
[3]Consultant Physician, Nagpur.

Address for Correspondence -
Dr. Parimal Tayde
E-mail : parimaltayde09@gmail.com

Acromegaly	Headache, acral enlargement, arthralgia, coarsening of face, amenorrhea, impotence, DM, HTN / CMP
Hyperthyroidism	Tremor, tachycardia, AF, weight loss, goiter, ophthalmopathy, pretibial myxedema
Hyperparathyroidism	Bones, stones, groans, moans
Hypothyroidism	Fatigue, cold intolerance, weight gain, nonpitting edema, periorbital puffiness
CAH : 11beta-hydroxylase deficiency	Ambiguous genitalia, Crisis in neonatal period, virilization , amenorrhea
CAH : 17alpha-hydroxylase deficiency	Genital ambiguity (male), sexual infantilism (Female), hypokalemia
Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis
Apparent mineralocorticoid excess	Growth retardation / short stature, hypertension, hypokalemia, DI
Pseudohypaldosteronism type 2	Short stature, hyperkalemic metabolic acidosis, normal aldosterone
Glucocorticoid Resistance Syndrome	Ambiguous genitalia, precocious puberty, hirsutism, oligo / an ovulation

In this review, we will focus on the common causes of endocrine hypertension.

Primary Hyperaldosteronism :

Primary hyperaldosteronism is now the most common cause of endocrine hypertension and it accounts for 5%-13% of the cases in population with age of onset between 30 and 60 years[2]. It exists mainly in two different forms, i.e. Idiopathic Hyperaldosteronism involving hyperplasia of bilateral adrenals, and, Aldosterone producing adenoma, classically described as Conn's Syndrome. IHA accounts for 60%-66% of the cases whereas. APA makes up the majority of remaining cases of primary hyperaldosteronism (30%-35%)[3]. Rest causes are rare.

Patients usually present with difficult to control hypertension and hypokalemia. It may be accompanied by metabolic alkalosis, muscle weakness, cramps, and polyuria. Hypokalemia may be unmasked by diuretics. However hypokalemia is present in only up to 37 % of the patients so it is not a must for diagnosis[4].

The screening for PAH should be considered in certain clinical situations. The endocrine society criteria for screening[5] are given in ***Table 2***.

Table 2 : Screening for Primary Hyperaldosteronism

Patients with sustained BP above 150/100 mmHg or > 140/90 mmHg on 3 drugs or < 140/90 on four or more drugs
Spontaneous or diuretic induced hypokalemia
Hypertension and adrenal incidentaloma
Hypertension and sleep apnea
Family history of early onset hypertension or cerebrovascular accident at a younger age (<40 yrs)
All hypertensive first degree relatives of patients with Primary Aldosteronism.

Initial screening of suspected patients should be conducted with a morning plasma aldosterone and renin activity levels. The aldosterone Renin Ratio is the most reliable means available for screening. Samples are collected in the morning, after patients have been out of bed for at least 2 hours, usually after they have been seated for 5-15 minutes[5]. Ideally, patients should have unrestricted dietary salt intakes before testing and should be potassium replete. In particular, mineralocorticoid receptor antagonist should be withdrawn for at least four weeks before testing. (5) Plasma aldosterone to plasma renin activity ratio of more than 30 ng/mL per hour and a plasma aldosterone of more than 20 ng/dL combination is 90% sensitive and 91% specific, with a positive predictive value of 69% and negative predictive value of 98%[6].

The Endocrine Society practice guidelines suggest verapamil, hydralazine, prazosin hydrochloride, doxazosin and terazosin as alternatives during screening because of their minimal impact on screening assays[5]. Patients with positive ARR should undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis. There are 4 tests for confirmation. They are Oral salt load test, Saline Infusion test, Fludrocortisone suppression test, and Captopril challenge test. Saline infusion test is commonly done. It involves the infusion 2 L of normal saline over 4 h and drawing plasma aldosterone level post infusion. Plasma aldosterone levels above 10 ng/dL is diagnostic of primary aldosteronism.

After biochemical confirmation CT scan or MRI of Adrenals is obtained for further evaluation to localize unilateral or bilateral source of aldosterone excess. When the nodules are small, undetectable or bilateral, adrenal venous sampling is needed to localize the source of hormone excess.

Management of Primary Aldosteronism - Medical management is needed in all patients with demonstrated bilateral disease. Patients with unilateral disease who do not undergo surgery are also candidates for medical management. The main stay of treatment of PAH is spironolactone, a competitive aldosterone receptor antagonist[7]. Patients usually require a dose of 50 - 400 mg/day with monitoring of blood pressure and potassium levels closely. It should be titrated slowly until blood pressure is controlled to a maximum dose. Side effects are gynecomastia, decreased libido, muscle cramps, erectile dysfunction, menstrual irregularities and loss of axillary hair[8].

Eplerenone is a selective aldosterone receptor antagonist, has fewer side effects as compared to spironolactone but is more costly. For patients with unilateral source of aldosteronism, laparoscopic adrenalectomy is now becoming treatment of choice & is indicated once potassium and blood pressure are controlled. ***Figure 1*** shows adrenal adenoma on left side in a patient with Conn syndrome.

PHEOCHROMOCYTOMA:

Pheochromocytoma is a tumor of the adrenal medulla that secretes epinephrine, norepinephrine, and dopamine. Paraganglioma is a tumor derived from extra-adrenal chromaffin cells of the sympathetic nervous system. It is located along the sympathetic chain in the head neck trunk or pelvic region. Pheochromocytomas and paragangliomas account for 0.2%-0.6% of all causes of hypertension in the population[9].

The average age of presentation of pheochromocytoma is approximately 4050 years with equally distribution between men and women[10]. The classic triad for"pheochromocytomaparoxysm" comprises of episodic headache, sweating and tachycardia. It is not always present[11]. (The most common sign, found in about 80%-90% of patients with pheochromocytoma, is hypertension[12].

Around 50% of the patients with pheochromocytoma present with sustained hypertension and 45% present with paroxysmal hypertension. Remaining 5-15 % of the patients may be normotensive[13].

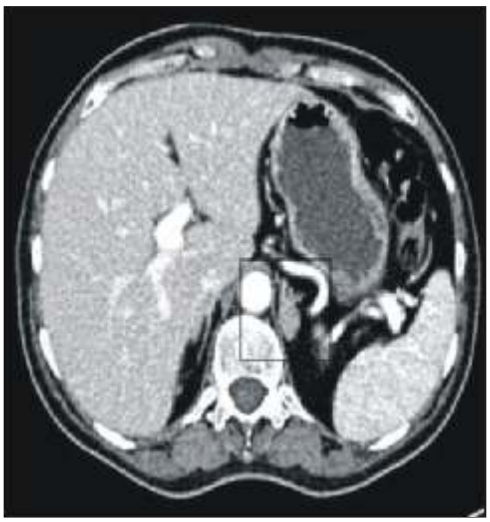
Paroxysm or "spell" can be triggered by physical activity (exercise or postural changes) as well as from tumor manipulation[13]. Other clinical features of pheochromocytoma include orthostatic hypotension due to volume depletion and

vasoconstriction,, pallor and anxiety, feeling of doom, generalized sweating, fever, nausea or vomiting, secondaryery throcytosis, new onset diabetes mellitus and isolated dilated cardiomyopathy are also associated with pheochromocytoma[14].

The cornerstone for diagnosis of pheochromocytoma is the measurement of urine and plasma fractionated metanephrines 24 hr. Urinary metanephrine and normetanephrine has sensitivity of 98% and specificity of 97%.Urinary VMA is an obsolete test now. Plasma catecholamines or urinary catecholamines are other not routinely available test.

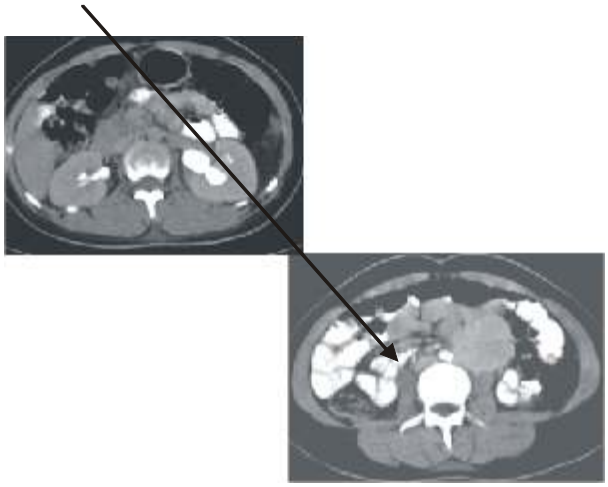
After biochemical confirmation of the diagnosis, localization of the lesion is done with imaging. CT Scan or MRI of the abdomen is usually the first investigation. Ninety-five percent of tumors are within the abdomen and pelvis and 10% of tumors are extra-adrenal. ***Figure 2*** shows CT abdomen showing an adrenal & extra adrenal mass which was a pheochromocytoma & paraganglioma

Figure :1



Showing Extra adrenal mass Left Adrenal adenoma in a patient with Conn Syndrome.

Figure : 2



Functional imaging can be done by MIBG, 18F-fluorodopamine, 18F-dihydroxyphenylalanine (DOPA), and 18F-FDG (FDG). FDG-PET is more sensitive than 123I-MIBG and CT/MRI for detection of metastatic disease[16].

Management - The medical management is aimed at normalization of blood pressure, heart rate, restoring volume depletion and prevention of intraoperative crisis.

Phenoxybenzamine is a noncompetitive, long acting, non-selective, and irreversible alpha-receptor blocker. It is usually started at a dose of 10 mg twice a day with increments of 10-20 mg every 2-3 d until clinical symptoms are controlled or patient develops side effects. This usually takes 7-14 days. Maximum dose is 1mg/kg per day[17]. The side effects of this medication are postural hypotension with tachycardia, dizziness, syncope and nasal congestion. Selective, short acting, and competitive alpha-blockers like doxazosinor, prazosin are preferred by some clinicians because they are associated with less reflex tachycardia and a lower incidence of postoperative hypotension when compared to phenoxybenzamine. Patients are also advised to take salt liberally to counteract the volume depletion. Preoperatively 2 liters of normal saline is infused to expand intravascular volume & to prevent post operative hypotension.

Once optimal α-blockade is achieved, β-blockers are initiated. They should not be used in the absence

of α-blockers as they will exacerbate vasoconstriction and hypertension by blocking the vasodilator component (β2). The most commonly used β-blockers are the non-selective β-receptor blocker propranolol (20-40 mg - 3 times a day) and the cardio selective β-1 blockers atenolol (25-50 mg per a day)[17]. Calcium channel blockers are the second line anti-hypertensive medications use to supplement α-blockers[18]. The drugs used are amlodipinein a dose of 10-20 mg, Nicardipine in a dose from 60-90 mg per day, Nifedipine SR in a dose of 30-90 mg and Verapamil SR in a dose from 180-540 mg per day[19]. Metyrosine (alpha-methyl-para-tyrosine) is a competitive inhibitor of tyrosine hydroxylase (dose of 500 mg to 3 gm per day) used in patients with extensive metastatic disease or large tumor burden[20]. This medication depletes the catecholamine stores after 3 days of treatment.

Intra-operative management - Patients may have wide fluctuations in blood pressure intraoperatively. IV Nitroprussideis a preferred vasodilator for intraoperative control of hypertension due to its rapid onset and short duration of action. Hypertensive crisis is managed by Nitoprussiude or short acting alpha antagonist Phentolamine. Infusing two liters of Normal Saline on day of surgery prevents postoperative hypotension. It can be treated by volume expansion, infusing crystalloids & vasopressors.

Regular blood pressure monitoring and optimal management of hypertension should be done. Surgical removal of pheochromocytoma does not always lead to cure of hypertension. Although 80% of patients become normotensive, postoperative hypertensionmay persist due to residual tumor, metastatic disease or intra operative injury to the renal artery or most commonly due to vascular changes due to long standing pre-operative hypertension.

Cushing's Syndrome

In Cushing syndrome hypertension is a common feature along with stria, bruises, proximal weakness and central obesity. Hypercortisolemia is associated with hypertension in approximately 80% of adult cases and half of children with Cushing syndrome. For establishing the diagnosis, the initial screening tests include Overnight dexamethasone suppression test. Once the screening test is positive, Low dose dexamethasone suppression test is carried out. High dose dexamethasone suppression test can be used for differentiating pituitary and ectopic Cushing. Midnight ACTH levels > 22pg/ml are suggestive of ACTH dependent cause whereas < 5 pg/ml indicates ACTH independent cause. For ACTH dependent cases, further evaluation is needed with pituitary imaging or inferior petrosal sinus sampling (I.P.S.S.), if adenoma is not detected in the imaging. MRI of brain / CT scan of chest & abdomen are needed to ascertain the diagnosis. As 90 % of the cases are due to pituitary microadenoma, trans sphenoidal surgery (T.S.S.) is the definitive treatment.

Acromegaly - Acromegaly is a growth hormone excess state usually due to GH secreting pituitary macroadenoma. It is characterized by acral (distal) enlargement, coarsening of facial features, fatigue, arthralgia, headache, and visual disturbances. Hypertension is seen in 60-70 % of cases. Non-suppressible post glucose GH levels > 1 ng/ml are suggestive of GH excess state. MRI Pituitary is needed to localize tumor and see suprasellar, parasellarextension. Surgery is the primary line of management.

Hyperthyroidism - Hyperthyroidism leads to increase in systolic blood pressure by increasing heart rate, decreasing systemic vascular resistance, and raising cardiac output. Elevated systolic blood pressure, low diastolic blood pressure and wide pulse pressure is seen in thyrotoxicosis.

Hypothyroidism : Hypothyroid patientsusually have elevated diastolic blood pressure.

Congenital Adrenal Hyperplasia : 11β-hydroxylase Deficiency

Virilizing and hypertensive forms of CAH can present in early childhood. It is characterized by elevated 11-deoxycortisol and DOC.

CAH : 17 α-hydroxylase Deficiency : This enzyme deficiency isextremely rare and leads to diminished

production of all adrenal hormones. Patients present with sexual infantilism, hypertension with hypokalemia. Females usually present with primary amenorrhea.

Apparent Mineralocorticoid Excess : It is an autosomal recessive disorder caused by deficiency of the 11 beta-hydroxysteroid dehydrogenase type 2 (11 beta-HSD2) enzyme. This enzyme converts cortisol to the inactive cortisone in renal tubular cells. It manifests with failure to thrive, polyuria and hypertension. Young patients with hypertension and family history of early stroke is a usual presentation. The biochemical abnormalities are hypokalemia, low PRA,low plasma aldosterone concentration and normal plasma cortisol. Acquired form of this condition is documented with licoriceuse which inhibits the activity of 11 beta-HSD2.

Liddle Syndrome :

It is an autosomal dominant disorder characterized by severe hypertension, hypokalemia, and metabolic alkalosis, low PAC and PRA and normal serum cortisol. It is due to "Gain of function" mutations in the genes coding for the beta-or gamma-subunit of the renal epithelial sodium channel, located at chromosome 16p13, which leads to constitutive activation of renal sodium resorption and subsequent volume expansion. Failure to respond to spironolactone or dexamethasone but response to amiloride or triamterene suggests the diagnosis of liddle syndrome.

Conclusion :

In summary, most of the causes of endocrine hypertension are treatable. A high index of suspicion, along with a systematic approach to diagnosis, localization is very important for successful management of these conditions. A multidisciplinary approach with team of internists, endocrinologists, radiologists and surgeons is recommended in optimal management of these conditions.

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