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# Clinical Presentation, Diagnosis, and Management of Primary Aldosteronism and Pheochromocytoma

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## Abstract

Primary hyperaldosteronism (PA) or Conn's syndrome and pheochromocytoma (Pheo) are functioning tumors of the adrenal glands that can cause secondary hypertension. Bilateral adrenal hyperplasia and aldosterone-producing adrenal tumor are the most common causes of PA. Due to the high circulating aldosterone, hypokalemia results which cause weakness, tingling sensation, muscle spasms, and periods of temporary paralysis. Pheo is a rare adrenomedullary tumor that can synthesize, metabolize, store, and secrete catecholamines and their metabolites. A high index of clinical suspicion remains the pivotal point to initiate biochemical studies for Pheo, particularly in those patients with a certain pattern of blood pressure elevation (paroxysmal or alternating with hypotension), drug-resistant hypertension, sudden palpitations (in some patients accompanied by pallor), unexplained sweating, especially during night or in cold weather, and unexplained hyperglycemia. Only after PA and Pheo are biochemically established should imaging be performed. The current imaging modalities include anatomical (computed tomography [CT] and magnetic resonance imaging [MRI]) and functional (molecular) imaging procedures using various radiopharmaceuticals depending on the clinical situation. For equivocal imaging results in PA, bilateral adrenal venous sampling is the "gold standard" to distinguish unilateral from bilateral lesions. Prompt diagnosis is important because delay in the diagnosis and treatment can lead to untoward cardiovascular complications including myocardial infarction, strokes, and fatal arrhythmias. Clinicians must be trained to have the "clinical eye" and awareness of early detection and management of these two curable causes of secondary hypertension.

**Key words:** Conn's syndrome, pheochromocytoma, primary aldosteronism, resistant hypertension, secondary hypertension

## Introduction

Primary hyperaldosteronism (PA) or Conn's syndrome and pheochromocytoma (Pheo) are functioning tumors from the adrenal glands that can cause secondary hypertension.[1,2]

Conn's syndrome is the excess production of the hormone aldosterone from the zona glomerulosa of the adrenal glands. The prevalence of PA has been reported to range from 4.6 to 9.5% among hypertensive individuals.[3,4] The high circulating aldosterone results in hypokalemia which leads to weakness, tingling, muscle spasms, and periods of temporary paralysis.[4,5] Bilateral adrenal hyperplasia and aldosterone-producing adrenal tumor are the most common causes of PA.[6]

Pheochromocytoma (Pheo) is a rare adrenomedullary tumor with an incidence of 0.1–0.6%.[1,7] About 0.05–0.1% of Pheo cases are undiagnosed in autopsy studies.[8] These tumors can synthesize, metabolize, store, and secrete catecholamines and their metabolites.[9] Pheos originate from adrenomedullary chromaffin cells that commonly produce epinephrine, norepinephrine, and dopamine. Chromaffin cells evolve into 80–85% Pheos and 15–20% are paragangliomas.[10]

A high index of clinical suspicion remains the pivotal point to initiate biochemical studies, particularly in those patients with a certain pattern of spells, blood pressure elevation (paroxysmal or alternating with hypotension), drug-resistant hypertension,

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sudden palpitations (in some patients accompanied by pallor), unexplained sweating, especially during night or in cold weather, unexplained hyperglycemia, and a hereditary predisposition for Pheo.[11]

Because PA and Pheo are caused by excess secretion of hormones from functional adrenal tumors, they are also called adrenal hypertension.

Only after PA and Pheo are biochemically proven, imaging should be performed.[6,10] The current imaging modalities include anatomical (CT and MRI) and functional (molecular) imaging procedures using various radiopharmaceuticals depending on the clinical situation. For equivocal imaging results, bilateral adrenal venous sampling is the "gold standard" to distinguish unilateral from bilateral lesions in PA.[6]

Although biochemical testing for PA and Pheo is indicated for symptomatic patients, it is also indicated for patients with incidentally found adrenal lesions. Silent PA and Pheo occur in 2.5–6% and 7–11% of adrenal tumors, respectively.[12]

Moreover, there are identified genetic predispositions or syndromic presentation pointing toward a high likelihood to develop PA and Pheo. In PA, these are patients with familial hyperaldosteronism type I, II, and III, KCNJ5 gene, CACNA1D gene, and multiple endocrine neoplasia type 1.[6] In Pheo, these are patients with von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), mutations of the succinate dehydrogenase genes (SDHB, SDHD), multiple endocrine neoplasia type 2 (MEN2), and hypoxia-induced factor 2A (HIF2A)-related Pheo-polycythemia syndrome.[13,14]

Delay in the diagnosis and treatment leads to untoward cardiovascular (CV) complications, namely myocardial infarction, strokes, fatal arrhythmias, chronic kidney disease, and death, compared with age-, sex-, and blood pressure (BP)-matched essential hypertensives among PA patients.[15] In Pheo, fatal tachyarrhythmia, myocardial infarction, stroke or death, and impaired myocardial function persisting even after normalization of catecholamine levels postoperatively have been reported.[16] Recently, systemic hormonal unloading for PA and PHEO has demonstrated to be beneficial as far as improvement in the CV function and quality of life is concerned.[16-19]

Clinicians must be trained to have the "clinical eye" and awareness of early detection and management of these two (PA and Pheo) curable causes of secondary hypertension to have significant lowering of morbidity and mortality. This is the objective of this concise review.

### Clinical Presentations

Silent PA and Pheo or incidentally found tumors occur in 2.5–6% and 7–11% of adrenal tumors, respectively, in both clinical and surgical studies.[11]

### Primary Aldosteronism

The clinical picture of PA (hypertension and hypokalemia) is attributed primarily to a resultant hypokalemia due to heightened mineralocorticoid effect of the excessive secreted aldosterone with water reabsorption and potassium urinary excretion in exchange of sodium. On top of high blood pressure, patients complain of weakness, tingling sensation, numbness, difficulty in doing activities such as putting on shirts, climbing up the stairs or getting in or off a vehicle, and even frank paralysis that often becomes the reason for emergency consult or admission.[3-6] Others have been reported to present already with CV complications such as stroke, severe arrhythmia, coronary heart disease, and myocardial infarction.[15] As reported by Mosso, hypertension can be mild (2%), moderate (8%), or severe (13%), among PA patients with hypertension.[20]

*Pheochromocytoma*

Symptoms associated with Pheo are often misinterpreted due to their similarities to other multisystem disease entities. Patients most commonly present with episodic attacks of elevated blood pressure, pallor, profuse diaphoresis, and palpitations.[11] Soltani *et al*. recently demonstrated that when considering a possible Pheo diagnosis, a clinical symptomatology likelihood ratio of headache, diaphoresis, and palpitations is shown to be significant.[21]

A specific catecholamine-receptor interaction characterizes the clinical picture of Pheo. Smooth muscles stimulation of α2-adrenergic receptors will result in arterial vasodilation and coronary vasoconstriction, and in Pheo, this typical manifestation may include diaphoresis and orthostatic hypotension. Stimulation of β1-adrenergic receptors has a positive chronotropic and inotropic effect in the heart. This, together with the increased release of renin, can contribute to hypertension, palpitations, and tachycardia. Stimulation of β2-adrenergic receptors will induce vasodilation of muscular arteries and some common effects in Pheo include constipation and nausea. β3-adrenergic receptors in adipocytes induce lipolysis and can cause weight loss.[22] Recently, literature have been showing case reports of young individuals in their 20s, unsuspected to have Pheo, presenting with premature CV events, with one succumbing to heart failure. Interestingly, CV anatomic and functional abnormalities reverse after adrenalectomy.[11,22-24]

## Diagnostic Approaches

### Biochemical Testing

Hypertension and hypokalemia are clinical presentations that lead to investigate patients for PA.[6] Hypokalemia is present only in 9%–37% severe cases of PA. Half of the patients with PA and 17% of those with idiopathic hyperaldosteronism (IHA) had serum potassium concentrations of <3.5 mmol/L in a large single study. The absence of low potassium has a low negative predictive value for the diagnosis of PA and the presence of hypokalemia has low sensitivity.[6]

The sustained elevated circulating aldosterone due to autonomous adrenal lesions suppresses the renin-angiotensin system. The most reliable means available test for screening for

PA is the aldosterone-renin ratio (ARR) with a value of >20. No need for further confirmatory testing, if there is spontaneous hypokalemia, and there is plasma renin below detection levels plus plasma aldosterone concentration (PAC) of >20 ng/dL (550 pmol/L).[6]

In equivocal CT/MRI findings, adrenal venous sampling with cosyntropin stimulation is performed. To confirm successful catheterization, the ratio of cortisol concentrations from the adrenal veins and peripheral veins is utilized. The ratio of more than 5:1 with the continuous cosyntropin infusion protocol and more than 2:1 without cosyntropin use signifies good catheterization.[6,25]

Genetic testing is advised in patients with diagnosis of PA at a younger age (earlier than 20 years) and in those who have a family history of PA or stroke at age <40 years and younger, and for familial hyperaldosteronism type 1 (FH-I) (glucocorticoid remediable aldosteronism [GRA]). Testing for germline mutations in KCNJ5 causing familial hyperaldosteronism type 3 (FH-III) must be conducted on patients with same age groups.[6]

The characteristic clinical features of Pheo signals need for biochemical testing, especially if severe hypertension is occurring in the young. Plasma free or urinary fractionated metanephrine determinations are preferred for the diagnosis of Pheo.[10] In general, it is preferred that specific institutions must develop their own reference values. Plasma metanephrine, but not normetanephrine, was higher in men but reference interval did not differ. A 3-fold increase from the reference intervals from the package inserts of commercial kits is usually utilized to interpret biochemical results. Medications can mildly to markedly raised values for biochemical test results and, therefore, must be stopped 2 to 4 weeks before testing. These are acetaminophen, mesalamine, sulfasalazine, and tricyclic antidepressants.[9-11] Dietary restrictions for a tyramine-rich diet (cheese, nuts, cereal, beer, and wine) are made mainly for the measurement of 3-methoxytyramine, a dopamine metabolite, and blood sample must be collected after an overnight fast. Stabilization of comorbidities is imperative to avoid false low (renal failure) or inadvertently high values (decompensated heart failure, stroke, and obstructive sleep apnea). Plasma metanephrine has shown to be least affected by these conditions.[9,11]

Global metabolite profiling, or simply metabolomics, is a new technology of functional genomics used for investigating metabolite changes associated with some gene mutations. Recently, a new technique, the so-called 1H high-resolution magic angle spinning (HRMAS) nuclear magnetic resonance (NMR) spectroscopy has been employed with the advantages suited for a small sample of tissues.[13,26]

Pheo can be part of several syndromic entities with genetic mutations such as VHL, neurofibromatosis type 1 (NF1), mutations of the succinate dehydrogenase genes (SDHB, SDHD), MEN2, and HIF2A-related PHEO-polycythemia syndrome.[13,14] Genotype-phenotype correlations have recently been shown, including a high risk of metastatic disease development, and therefore, Pheo patients presenting with such must be tested.[10]

**Imaging Modalities**

In patients with suspected secondary hypertension, such as PA and Pheo, a positive biochemical workup must be shown before any imaging procedures are initiated.[6,10]

In PA, adrenal computed tomography (CT) is the initial imaging tool to look for possible adrenocortical adenoma and to provide landscape for radiologists and surgeons.[6] For small PAs, bilateral nodularity or normal-appearing adrenals interpretation must be done with ample caution. For detecting unilateral aldosterone, excess adrenal venous sampling yields better sensitivity and specificity (95% and 100%, respectively) compared with adrenal CT (78% and 75%, respectively)[6,25] MRI aside from being expensive has less spatial resolution than CT.[6]

Functional imaging procedures have been utilized to assess lateralization of actively secreting tumors.[27] Since its introduction in the 70s, an improved iodocholesterol scintigraphy agent, (6b-131I) iodomethyl-19-norcholesterol (NP-59), has demonstrated significant correlation of function with anatomical abnormalities, although the size of the adenoma affects its finding.[6] It is not reliable if tumor mass is 1.5 cm in diameter and rarely plays a role in subtype evaluation.[6,11] C-Metomidate positron emission tomography (PET)- CT is a good alternative to AVS in the management of PA with a reported specificity of 87% and sensitivity of 76%.[28]

Anatomic imaging with the use of CT has been the preferred initial procedure for localization of Pheos due to its high sensitivity of 90%.[10,29] However, its limitation has been observed in extra-adrenal, recurrent, and metastatic lesions. MRI, on the other hand, is more advantageous in detecting extra-adrenal lesions and is indicated in those with an allergy to contrast, pregnant, or pediatric patients, and those whose contrast medium is a contraindication.[16] Ultrasound sensitivity is poor but very useful in the detection of liver metastasis and lesions in the urinary bladder.[30]

As summarized by Mercado-Asis *et al.*, functional imaging offers the advantage of higher specificity in detecting multifocal and metastatic tumors and can characterize tumoral metabolic activity. I- or (131) I-metaiodobenzylguanidine (MIBG) scintigraphy has the structure similar to NE so it can enter cells through NE transporters. 123I-MIBG is more sensitive and has better detection rate.[11] On the other hand, single-photon emission computed chromatography has been used with CT/MRI for colocalization. MIBG is reserved for volume determination before 131IMIBG therapy for metastatic Pheo.[31]

PET is showing superiority in spatial resolution. 18F-fluorodeoxyglucose PET is the preferred procedure for malignant tumors, especially SDHB-related PHEO since cancer cells readily take up glucose. 18F-fluorodopamine (FDOPA) is a more specific tracer since its structure is similar to dopamine, a catecholamine precursor, and, therefore, enters the cell through NE transporter. This imaging modality has high sensitivity for metastatic tumors.[32] Newer PET scanning tracers have been developed and showed promising results in detection of metastasis and characterization of metabolic activity of

the tumor cells, namely the DOTA peptides – DOTATATE, DOTATOC, and DOTANOC (65). Ga-DOTATOC PET/CT was found superior to FDOPA PET/CT in the diagnosis of metastatic tumors.[11,13]

## Management

The control of hypertension and the removal of the adrenal lesion by unilateral adrenalectomy are the mainstay of the treatment for PA and Pheo.

Before patients with PA undergo surgery, both hypertension and hypokalemia should be well-controlled. Caution should be exercised in doing pre-operative barium enema in patients with PA since this may lead to another hypokalemic episode. The mineralocorticoid antagonist (MRA) spironolactone and potassium supplementation go together in the medical treatment of hypokalemia. Potassium supplementation must be withdrawn on post-operative day 1, together with the discontinuation of spironolactone, and reduction of antihypertensive therapy, if appropriate, to monitor success of surgical treatment.[6] To partially suppress pituitary adrenocorticotropic hormone (ACTH) secretion, glucocorticoid-remediable aldosteronism (GRA) should be managed with a glucocorticoid. The starting dose of prednisone is 2.5–5 mg/day whereas that of dexamethasone in adults is 0.125–0.25 mg/day. The glucocorticoid should be taken at bedtime to suppress the early morning ACTH surge.[6] Eplerenone, a selective MRA without antiandrogen and progesterone agonist effects,[33] *in vivo* has 50% of the MRA potency of spironolactone. It is well tolerated although known to be expensive.[6]

CV evaluation is an essential part of pre-operative management in Pheo because they are known to have compromised cardiac function such as subclinical left ventricular failure.[10] Appropriate medical management to decrease the left ventricular function may reduce the perioperative CV complications. For achieving effective α-blockade, both phenoxybenzamine and doxazosin, two α-adrenoceptor antagonists, are preferred[10] with broader experience with the non-competitive α-adrenoceptor blocker phenoxybenzamine. To achieve a stabile situation, 10–14 days of pharmacological pretreatment are advised. Calcium channel blockers have been found to be effective as monotherapy or in combination with α-adrenoceptor blockade.[10]

The posterior retroperitoneal approach with minimal invasive laparoscopic tumor resection is currently the standard approach of surgical management with Pheo.[10] For long-term outcome of operated patients, it is essential to have optimum follow-up for three reasons: (1) To see completion of surgery; (2) tumor recurrence; or (3) development of metastases, even after many years. To date, no pathologic criteria have been established to evaluate tumor benignity or malignancy nor preponderance for metastasis.[10,34] Biochemical evaluation with measurement of plasma or urine metanephrines at 2 to 6 weeks after surgery is recommended to ascertain success of operation. Since there is a risk of local or metastatic recurrences or development of new tumor in 5% of operated Pheo patients during 5-year follow-up, it is recommended to maintain postsurgical follow-up in all operated patients for at least 10 years. Lifelong follow-up is recommended to Pheo patients who are young, those with an extra-adrenal or large tumor, and those who with a germline mutation since they have a high tendency to recur.[10] Inhibition or alteration of certain metabolic processes involved in tumorigenesis is a very promising therapeutic approach.[13,35]

### Summary and Clinical Insight

Primary aldosteronism and pheochromocytoma are two common causes of secondary hypertension. Clinicians must have a high index of suspicion when confronted with difficult to treat or resistant types of hypertension, presenting with the symptoms associated with the two. A good "clinical eye" and increased awareness of their pathognomonic clinical presentations may help in the early detection and management of these two causes of adrenal hypertension. Early diagnosis and timely treatment are imperative to prevent long-term hypertension-mediated organ damage and irreversible complications on the cardiocerebrovascular and renal systems, thereby decreasing morbidity and mortality associated with primary aldosteronism and pheochromocytoma.

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