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Adrenal Incidentalomas and Functioning Adrenal Masses

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Objectives

1. Diagnosis, treatment and follow up of adrenal incidentaloma
2. Diagnosis, clinical picture, treatment and follow up of CS
3. Diagnosis, clinical picture, treatment and follow up of PA
4. Diagnosis, clinical picture and follow up of Pheochromocytomas and paragangliomas

Adrenal Incidentaloma Definition

- An adrenal mass discovered serendipitously by radiologic examination.
- In the absence of symptoms or clinical findings suggestive of adrenal disease.
- and > 1-cm in diameter (ie, leaving no question that it really is a mass).

Adrenal Incidentaloma--Prevalence

- With ↑ing resolution of CT, specific attention from radiologists, & more careful prospective studies, the prevalence of adrenal incidentalomas ↑ed from 0.6%* in 1982 to 7.3% in 2020*
- In a recent prospective study from Italy** over a 2-yr period (2017-2018) an incidental adrenal mass was found in 44 out of 601 (7.3%) unselected adults who had an abdominal CT scan (note: patients with suspected adrenal disease or those with a malignancy were excluded).
- Mass size: 1.0 5.0 cm (median 2.1 cm)

Adrenal Incidentalomas

Key Numbers to Remember

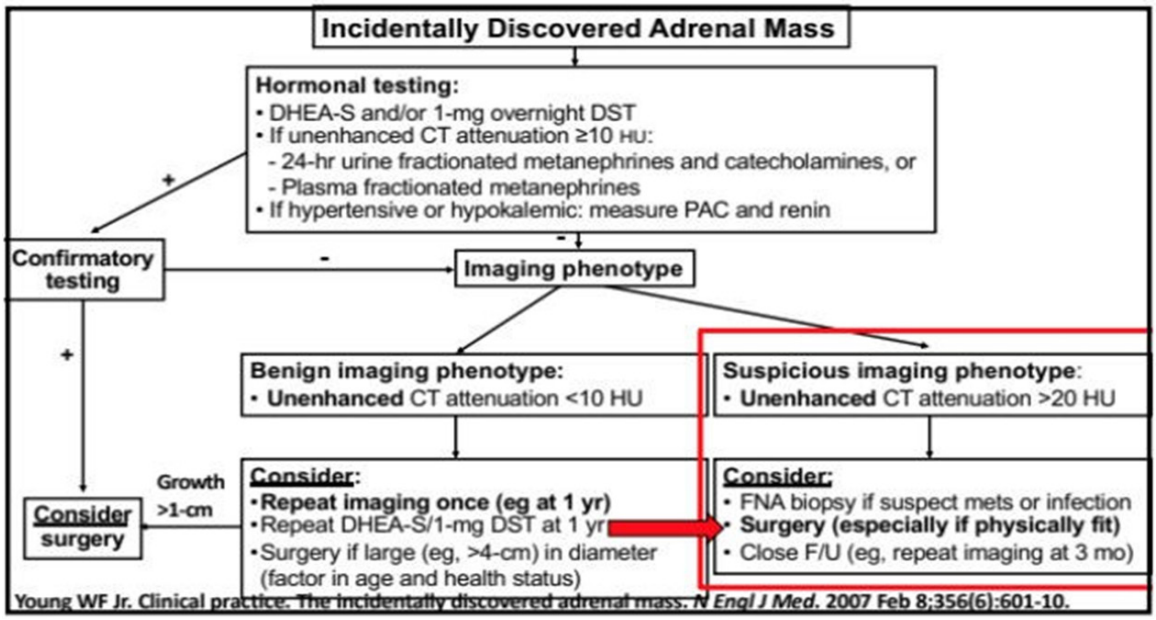
- 85% benign cortical adenoma
- 5% other benign adrenal masses (eg, myelolipoma)
- 5-8% malignant (metastatic, ACC)
- 1-3% pheochromocytoma

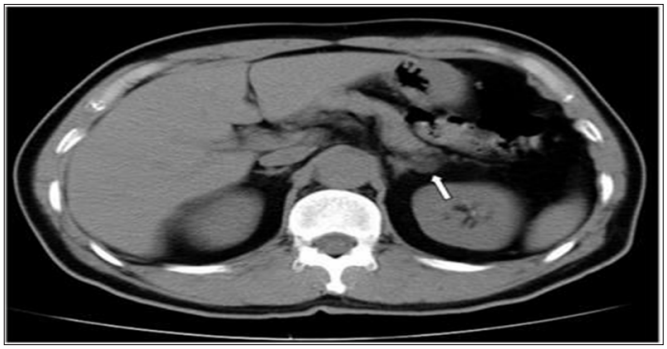
Diagnostic Strategy Characterize the Mass for Functional Status

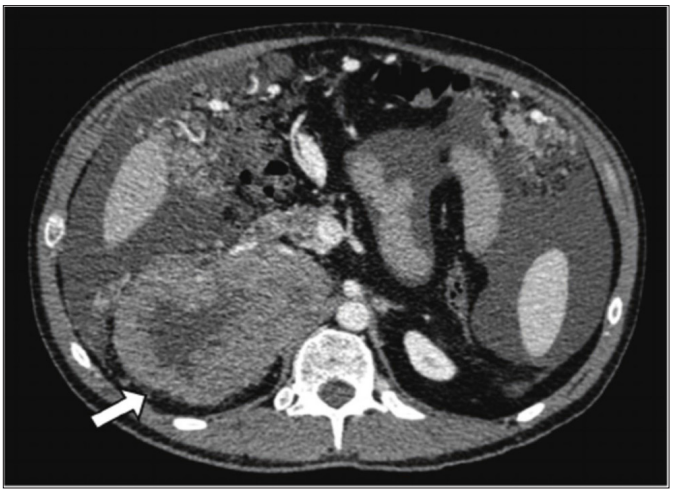
- History and physical exam
- Hormonal assessment

Diagnostic Strategy Characterize the Mass for Malignant Potential

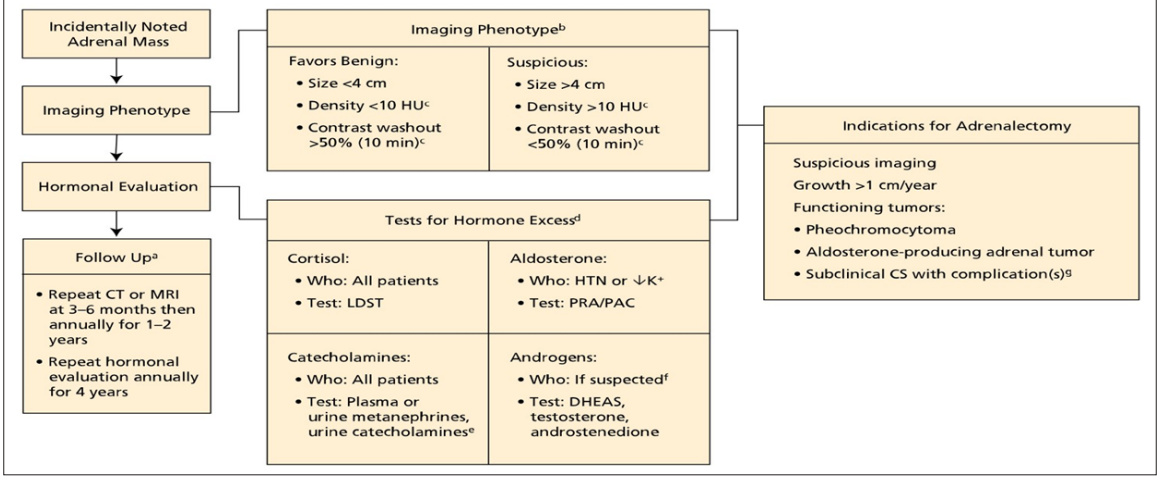
- Imaging Phenotype
- Size, growth, and history of extra-adrenal malignancy







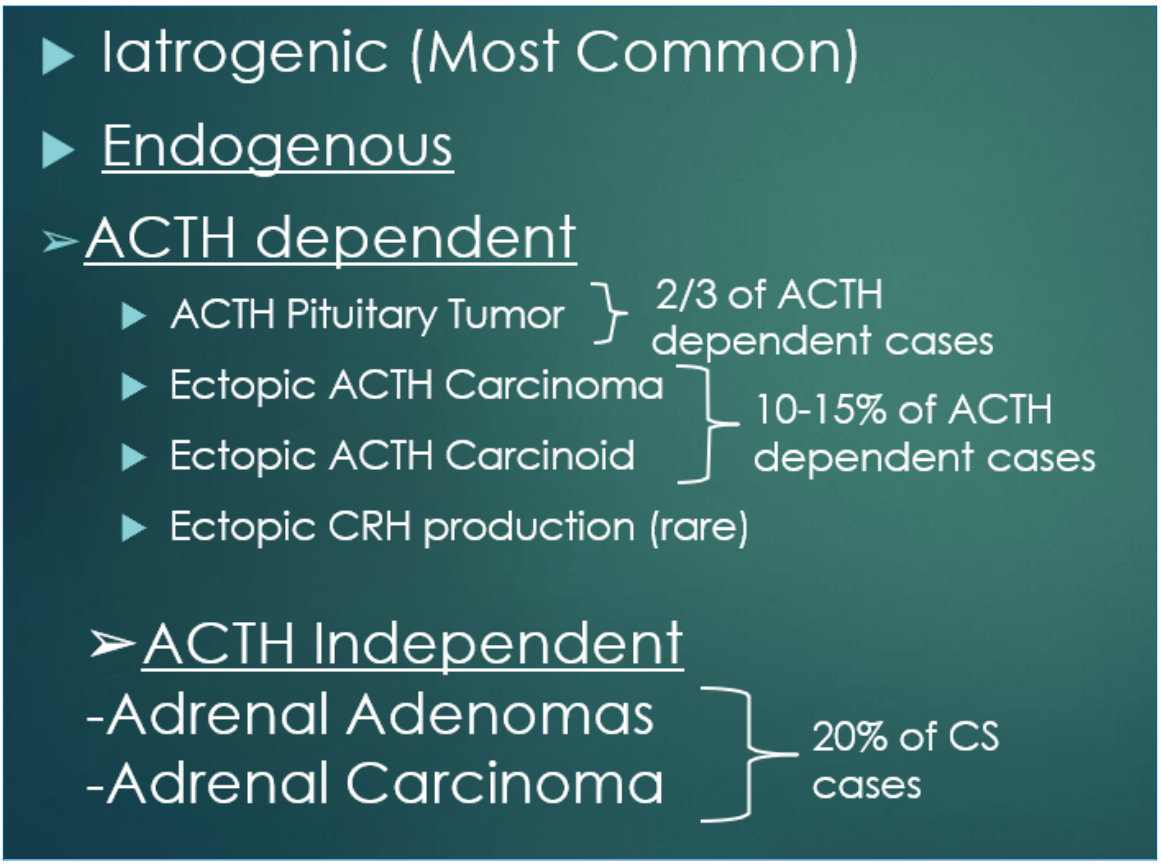
Algorithm for the initial diagnostic evaluation and follow up of an incidentally noted adrenal mass. CS = Cushing syndrome; DHEAS = dehydroepiandrosterone sulfate; HTN = hypertension; HU = Hounsfield units; K = potassium; LDST = low-dose (1-mg) dexamethasone suppression test; PAC = plasma aldosterone concentration; PRA = plasma renin activity.



Changed Guidelines

1. If mass is less than 4 sm, homogeneous, less than 10 HU, clear borders and no hormonal production no need for repeat imaging or hormonal follow-up!! New AACE guidelines!
2. If mass is indeterminate more than 10 HU- MRI for signal drop out or CT with contrast for 15 min-wash out. If no hormonal production and if the drop out of the signal on MRI or 15 min wash out on CT with contrast is more than 60%- suggests benign adenoma- no need for f/o if hormonally inactive. If the mass is not homogenous- Do PET scan – question of malignancy?
3. If subclinical CS- very rarely clinical CS , but mass might need to come out if worsening DM, HTN,OP or growth more than 0.5 sm - 1 sm per year.
4. If mass CT w/o contrast less than 10 HU – no need to r/o Pheochromocytoma.

Types of Cushing Syndrome



Other Causes of Hypercortisolism Pseudo-Cushing Syndrome

Must be differentiated from Cushing Syndrome – happens in the disease states listed below

- Obesity
- PCOS
- Anorexia Nervosa
- Depression
- Alcoholism
- Physical Stress (example: Infection)
- Hyperthyroidism
- Anxiety, Panic disorder, Obsessive-compulsive disorder

Epidemiology of Cushing Syndrome

Cushing Syndrome & Cushing Disease

- Incidence of 1.2-2.4/million per year in two European population-based study
- Commercial claims database in the US: incidence 8/ million per year
- 3-8 times more common in women
- A prevalence as high as 5% among patients with uncontrolled diabetes or osteoporosis in tertiary centers has been reported*.

Adrenal Cushing

- Incidence 0.8/million per year (adrenal adenoma & carcinoma)*

Ectopic ACTH syndrome

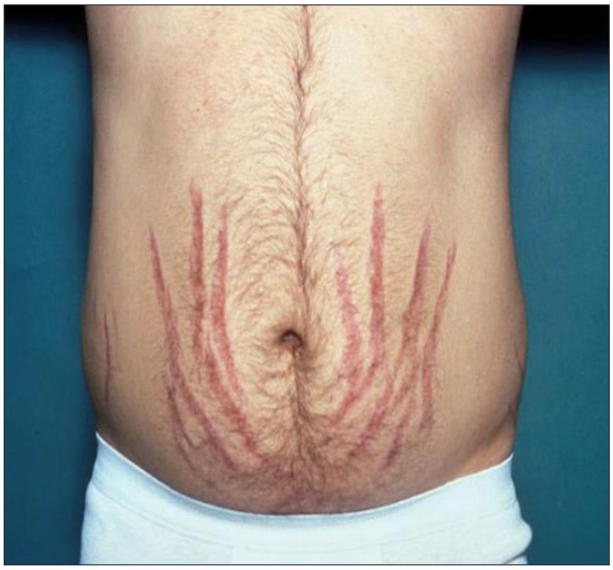
- Small cell lung cancer makes -50%

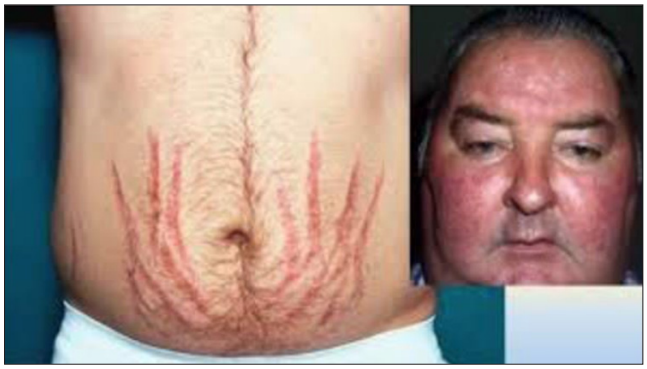
- The patients might have mild increase of urine free-cortisol in Pseudo Cushing Syndrome and blunted response to dexamethasone suppression. However there are no more reliable clinical features of hypercortisolism such as proximal muscle weakness, easy bruising, wide violaceous striae, facial plethora, supraclavicular and dorsocervical fat pads and the condition is reversible after stopping drinking ETOH, weight loss etc.
- Usually there is normal rhythmic secretion of cortisol with normal midnight salivary cortisol in Pseudo Cushing Syndrome. In Cushing Syndrome night salivary cortisol it is much higher

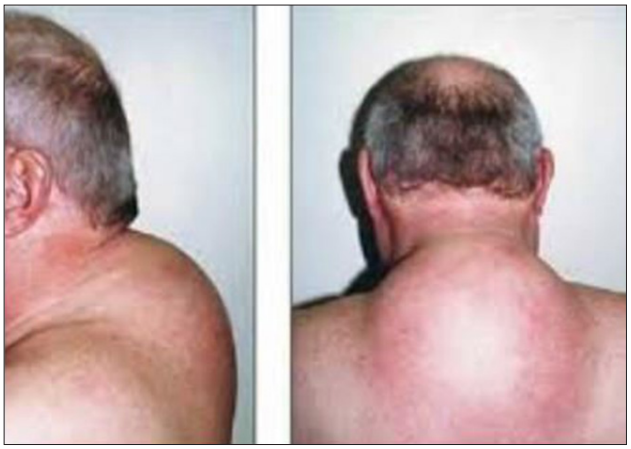
- CRH stimulation test – there is suppressed response of ACTH and cortisol in Pseudo-Cushing syndrome compared to Cushing's disease where there is a normal or increased response
- Also with low dose 48- hours dexamethasone suppression test followed in 2- hours after the last dose of Dexamethasone by CRH stimulation, then levels of cortisol above 1.4 mcg/dl is suggestive of Cushing's syndrome and lower in Pseudo- Cushing Syndrome
- In Pseudo-Cushing Syndrome there is mild hypercortisolism caused by chronic activation of HT-HP axis which is reversible after treatment of those conditions.

Clinical Manifestations

Clinical Features of Cushing Syndrome		
Specific Findings	Less Specific Findings	Associated Conditions
Centripetal obesity Facial plethora Supraclavicular fat pads Dorsocervical fat pads Wide violaceous striae	Easy bruising Excessive skin fragility Proximal muscle weakness Impaired memory Temporal balding Hirsutism (in women)[b] Menstrual abnormalities	Osteoporosis Hypertension Diabetes mellitus Obesity Depression Hypokalemia Nephrolithiasis VTE/PE







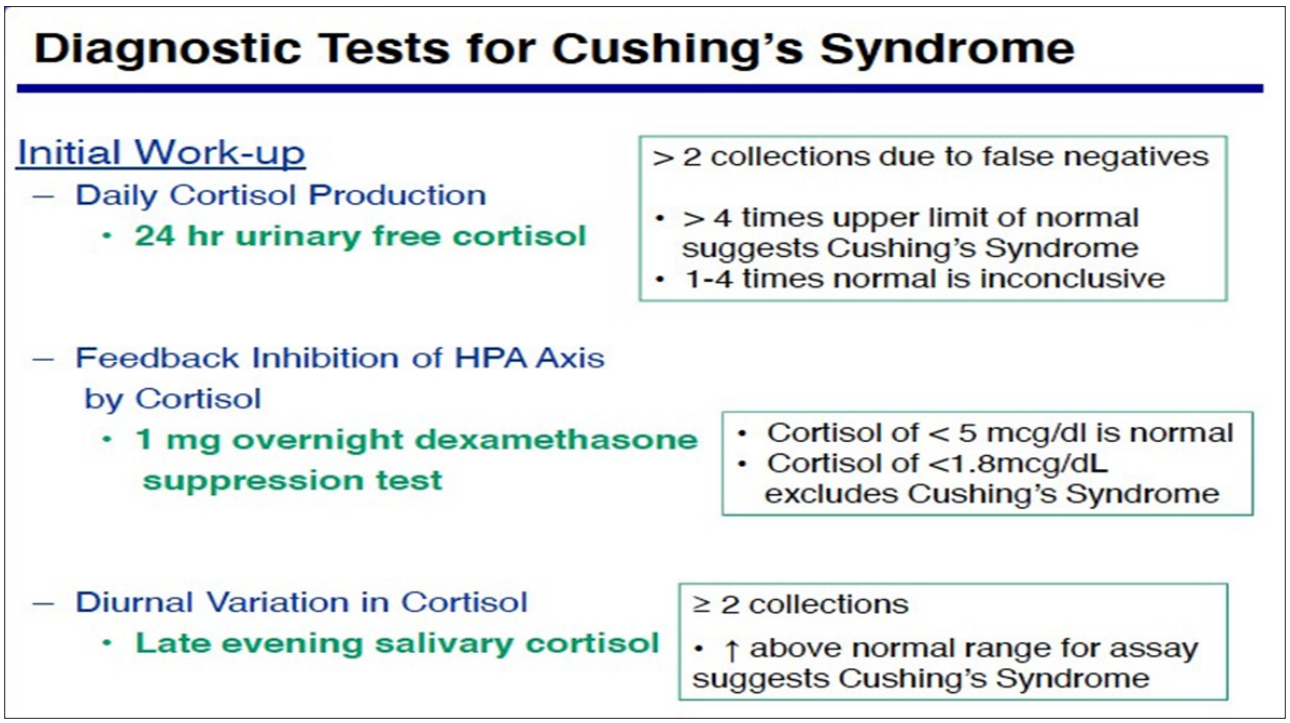
Ectopic ACTH Syndrome

Clinical Features

Similar incidence in men and women"
Rapid onset, Cushingoid habitus may be absent
Muscle wasting and hyperpigmentation frequent
Hypokalemia common

Differential diagnosis*

Small cell lung cancer up to 50%
Bronchial carcinoid 2-37%
Thymus tumors 8-12%
Pancreatic tumors 4-12%
Pheochromocytoma 5-12%
Medullary thyroid cancer 0-5%



Sensitivity, Specificity and caveats od screening test for Cushing's Syndrome

Test	Sensitivity	Specificity	Caveat
1 mg DST (<1.8 µg/dL)	91-97%	80-94%	CBG effect, Dex clearance
24-hr UFC	85-92%	45-98%	Improper collection, high fluid intake (>5 liters), CKD
LNSC	88-100%	82-100%	Improper collection, shift workers
2-day LDDST (<1.4 µg/dL)	90-100%	97-100%	CBG effect, Dex clearance
2-day Dex/CRH Test (<1.4 µg/dL)	98-100%	60-100%	CBG effect, Dex clearance

Sharma ST, et al. Clin Epidemiol. 2015;7:281-293

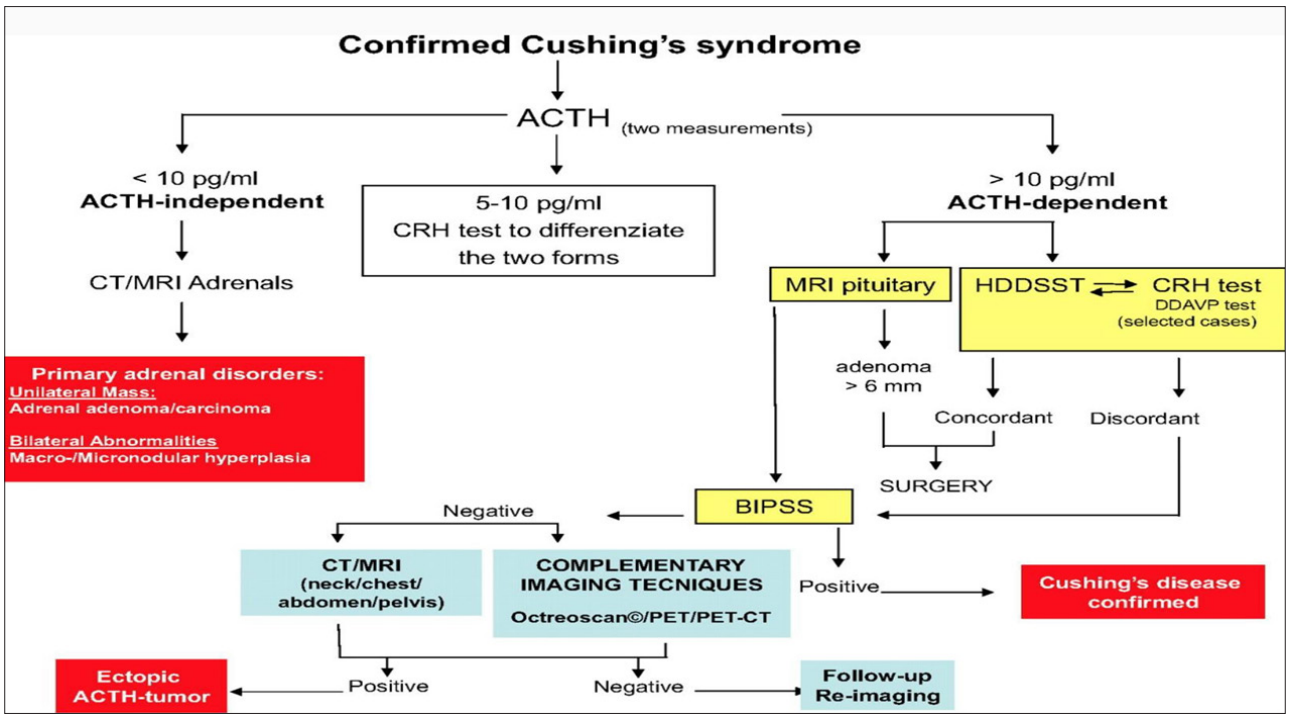
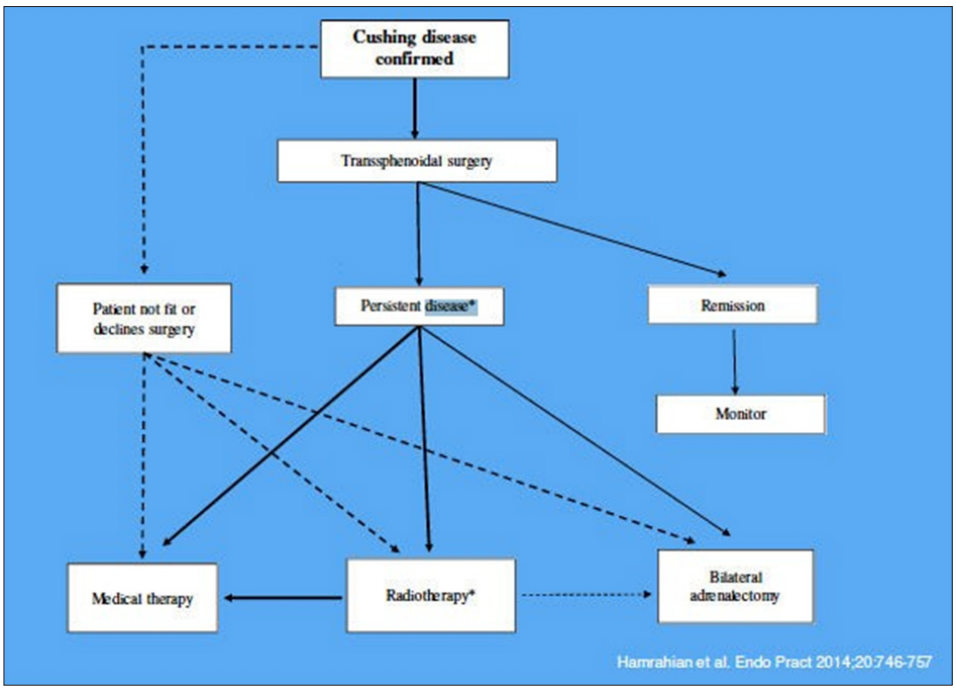


Table 2. Responses to CRH Testing [6]

Diagnosis	Corticotropin Response	Cortisol Response
Pituitary Cushing syndrome	Normal or increased	Normal or increased
Adrenal Cushing syndrome	Suppressed	Suppressed
Ectopic Cushing syndrome	Suppressed	Suppressed
Pseudo-Cushing syndrome	Suppressed	Suppressed
Pituitary Adrenal insufficiency	Suppressed	Suppressed



Ectopic ACTH Syndrome

Imaging

- CT neck/chest/abdomen
  MRI does not add much in most cases
- Gallium 68 Dotatate PET/CT***
- FDG-PET/CT (mostly helpful for showing the extent of metastatic disease)

Biochemical workup

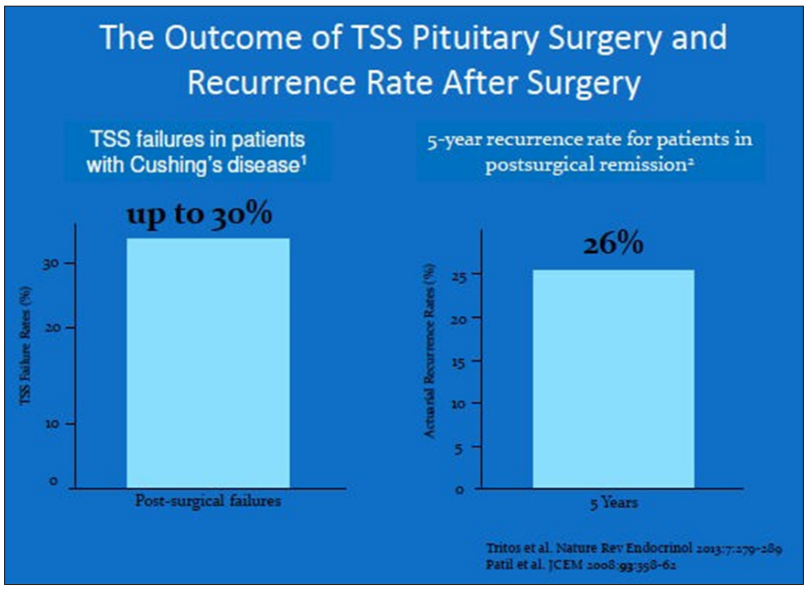
- Urine 5-HIAA, Calcitonin, metanephrines

Surgery is the treatment of choice

- Up to 20% of tumors can not be localized*
- Low threshold for bilateral adrenalectomy
- Medical therapy to control severe hypercortisolemia

Treatment of Cushing's Disease

- If clinical and testing results are consistent with Cushing disease, trans-sphenoidal surgery is the treatment of choice.
- Endogenous ACTH production in the remaining normal pituitary gland will be suppressed after removal of the tumor due to long- standing hyper cortisolism
- Patients with successful surgical treatment/ 8 a.m. cortisol less than 2 mcg/dl in 24-72 hours post surgery/ will have acute ACTH deficiency and require glucocorticoid replacement. It may take up to 1 year for endogenous ACTH production to return to normal, and sometimes the hypothalamic-pituitary-adrenal axis does not recover. After successful resection, Cushing disease can recur, and patients must be monitored annually for several years, and then less frequently, or sooner if symptoms of hyper cortisolism recur



Medical Therapies for Cushing Syndrome

ACTH inhibitors

- Cabergoline
- Pasireotide*

Adrenal steroidogenesis inhibitors

- Ketoconazole
  Levoketoconazole
- Metyrapone
- Osilodrostat*
- Etomidate
- Mitotane

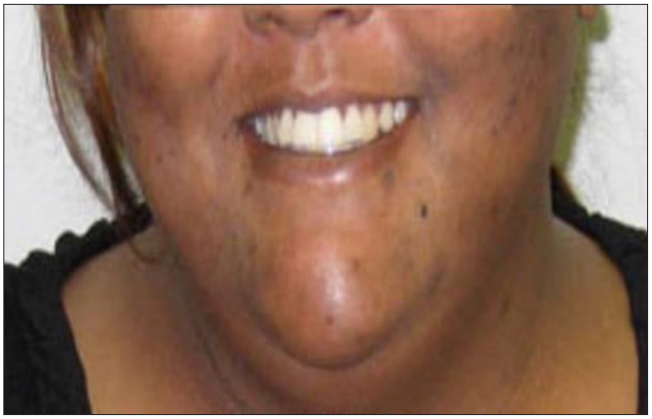
Cortisol receptor blocker

- Mifepristone (in the presence of hyperglycemia)*
  Relacorilant

Bilateral Adrenalectomy

Last line treatment of Cushing's disease is by bilateral adrenalectomy and glucocorticoid and mineralocorticoid therapy for life.

Nelson's syndrome: adverse result of bilateral adrenalectomy in patient's with Cushing's Disease. The procedure will stop cortisol production and provide relief; however, results in rapid growth of the pituitary tumor and associated hyper pigmentation, If not also radiation of the HP adenoma after the adrenalectomy. Treatment is with surgery or radiation of the pituitary tumor.



Picture of patient with Nelson's Syndrome with Hyperpigmentation

Adrenal Cushing Syndrome

- Adrenal adenoma
- Bilateral macronodular adrenal hyperplasia (BMAH)
- Primary pigmented nodular adrenocortical disease (PPNAD)
- Adrenocortical carcinoma (often secretes other hormones)

Autonomous cortisol secretion (subclinical Cushing Syndrome)

- 5-30% of patients with adrenal incidentalomas
- 1 mg DST is the preferred initial biochemical workup
- A low ACTH and DEHAS levels support the diagnosis.

Adrenocortical Carcinoma

ACC is a rare malignancy affecting 0.5 to 2 persons per million per year that is often associated with excessive production of adrenal hormones. Patients with ACC most frequently present with signs and symptoms related to hormonal excess. They may also experience symptoms related to local tumor growth (abdominal fullness, nausea, or back pain) or metastasis. ACC is sometimes detected incidentally when abdominal imaging is performed for another reason.

Autonomous secretion of adrenal hormones or their biologically inactive precursors is seen in more than 80% of patients with ACC (cortisol 50%; multiple hormones 20%; androgens 5% to 10%; aldosterone rarely). The pathologic diagnosis of ACC is challenging. Even tumors that appear to be low risk based on histopathology can occasionally be malignant. Patients with low-risk pathology but concerning imaging findings or tumors larger than 4 cm should have close interval radiographic follow up after surgery.

The prognosis of ACC is very poor; the 5-year survival rate for stage I disease is 65%, stage II 65%, stage III 40%, and stage IV less than 10%. Management depends on the extent of disease at presentation.

Open surgical resection is first-line treatment for early disease. Adjuvant radiotherapy to the tumor bed is used when resection is incomplete. Adjuvant medical therapy with mitotane, an adrenolytic drug, is recommended for patients with known or suspected residual or metastatic disease. Cytotoxic chemotherapy has poor efficacy. In addition to mitotane, inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, and etomidate) are used to treat CS, if present. Surgery for metastatic ACC is indicated if symptoms related to hormonal hypersecretion cannot be controlled with medical therapy alone. Percutaneous radiofrequency ablation may also be used to treat unresectable primary tumors or metastases when needed.

Treatment of ACTH-Independent Cushing's Syndrome Due to Adrenal Adenoma or Macro/Micro Nodular Adrenal Hyperplasia

- Recommendation is to normalize cortisol or its action at its receptors in order to eliminate symptoms
- 1st line therapy- Surgery, for Adrenal Adenomas
- For Macro and Micro nodular adrenal hyperplasia – bilateral adrenalectomy indicated with glucocorticoid and mineralocorticoid replacement for life. If one gland bigger than other consider first unilateral adrenalectomy.
- When surgery is delayed, treat with adrenal enzyme inhibitors (metyrapone, osilodrostat, ketoconazole, and etomidate in acute settings) or cortisol receptor antagonist mifepristone

Post Unilateral Adrenalectomy Due to Adrenal Adenoma or Carcinoma Care

Patients should be treated with stress-dose glucocorticoids during perioperative period and continued on physiologic replacement until HPA axis recovery confirmed.

Cushing Syndrome changes can take up to 1 year to resolve.

Primary Aldosteronism Once a Zebra, Now a Horse

What is Primary Aldosteronism?

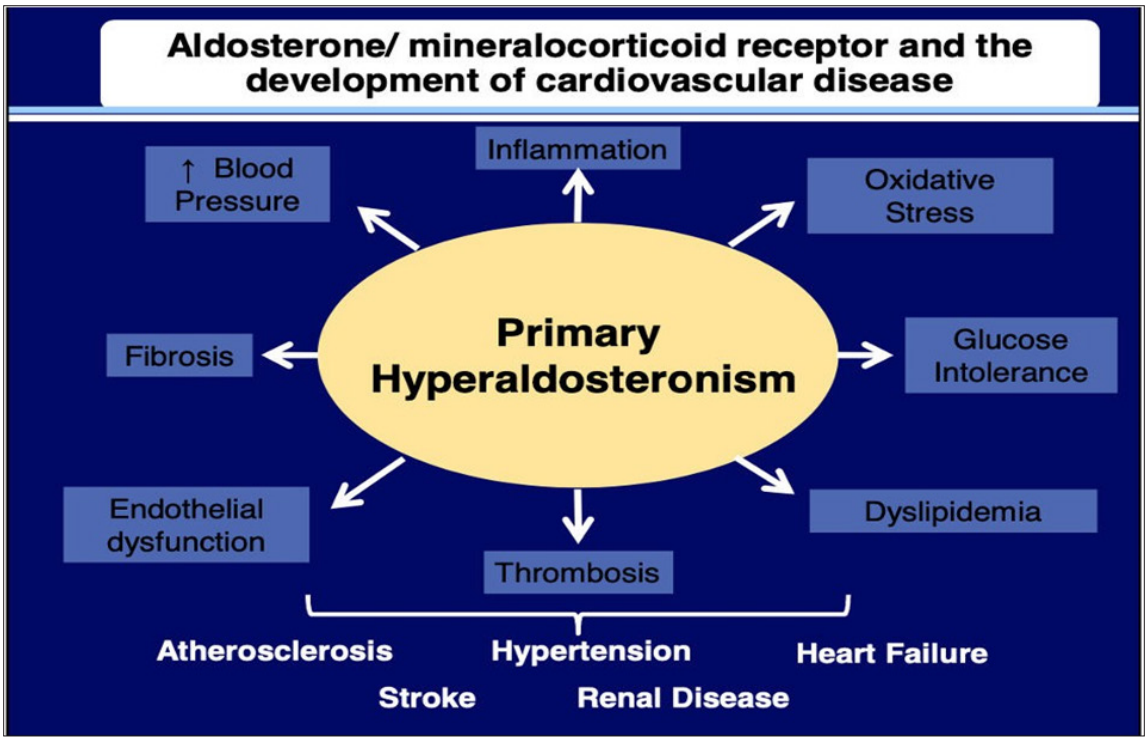
SYNDROME of Inappropriate, Relatively non-suppressible, Renin- independent aldosterone production that results in excessive activation of the renal-MR, vicious cycle of volume expansion => can increase BP, increases K+/H* excretion, increases risk for CV disease independent of BP (extra-renal MR).

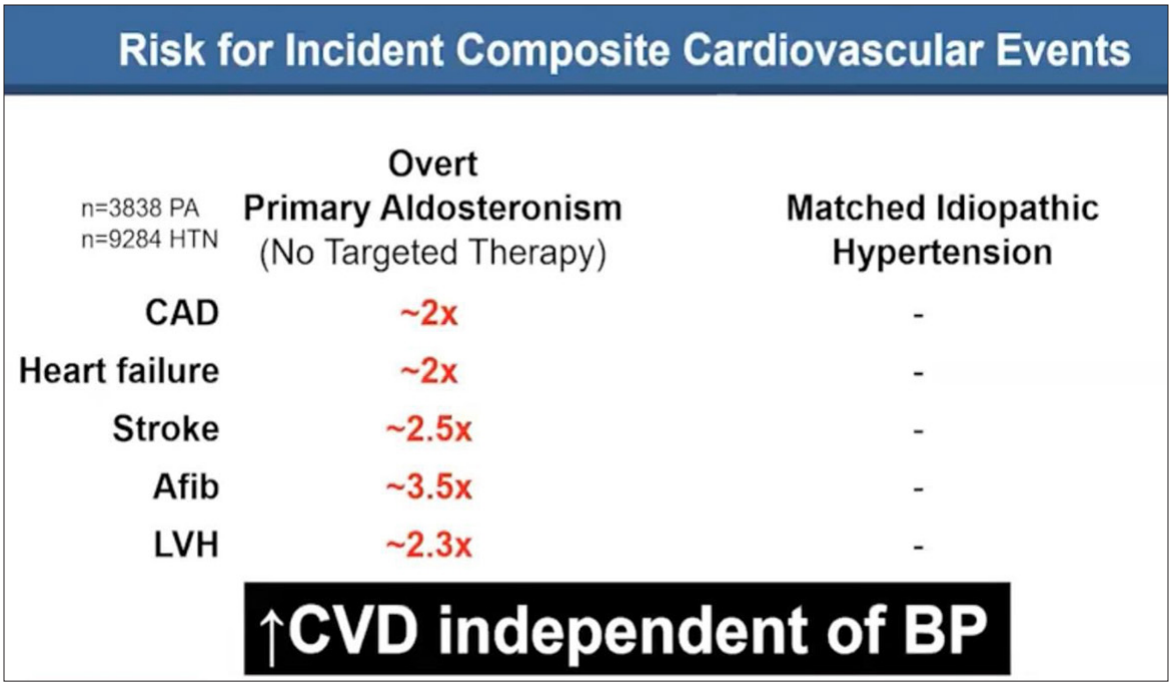
Clinical Manifestations

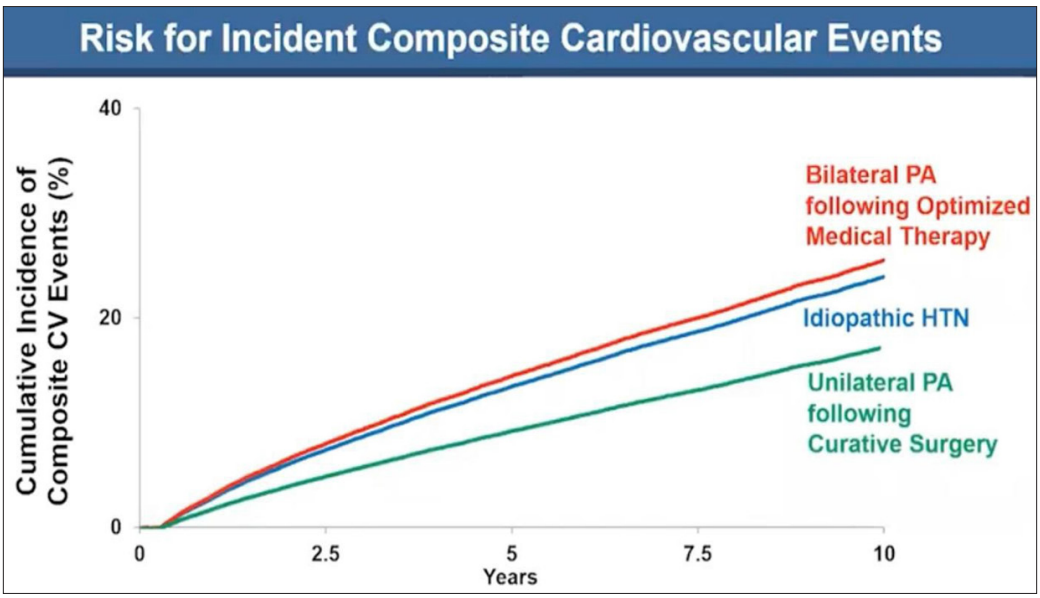
Reflect the severity and duration of the renin-independent aldosteronism BP and potassium are dependent features.

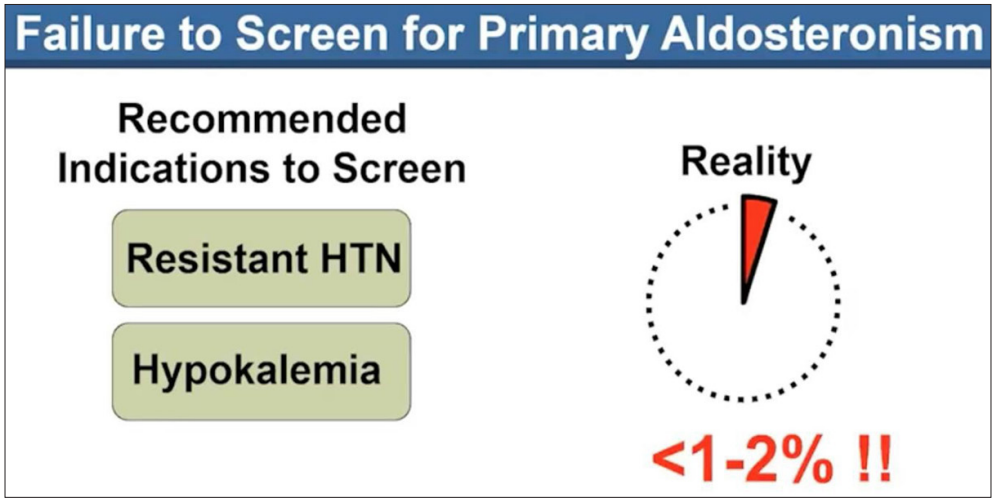
Why should you care?

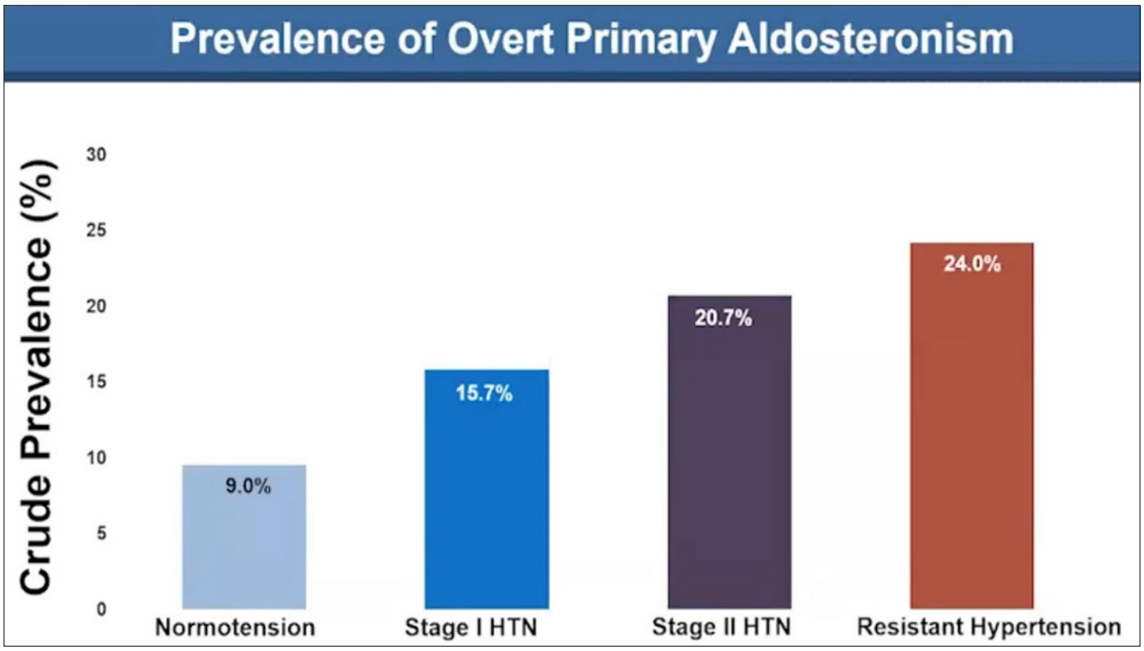
Part I : Preventable Cardiovascular Risk
Part II : Under-recognition
Part III : High Prevalence

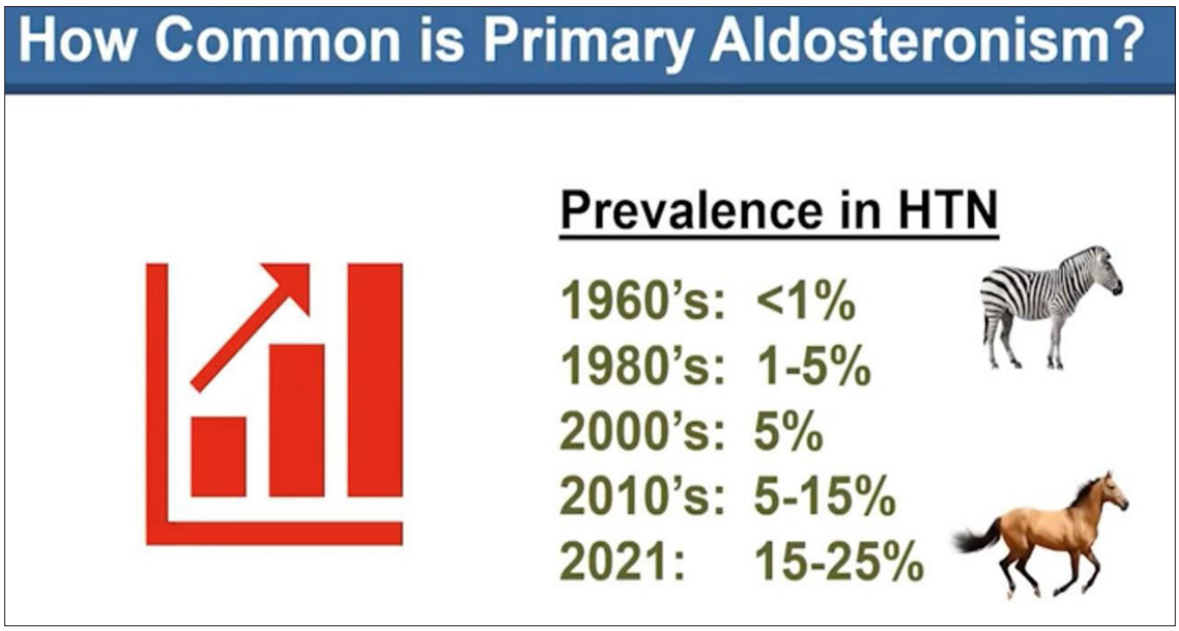





Risk for Incident Composite Cardiovascular Events
Cumulative Incidence of Composite CV Events (%)
40
20
0
0
2.5
5
7.5
10
Years
Bilateral PA following Optimized Medical Therapy
Idiopathic HTN
Unilateral PA following Curative Surgery


Failure to Screen for Primary Aldosteronism
Recommended Indications to Screen
Resistant HTN
Hypokalemia
Reality
<1-2% !!


Prevalence of Overt Primary Aldosteronism
Crude Prevalence (%)
30
25
20
15
10
5
0
9.0%
15.7%
20.7%
24.0%
Normotension
Stage I HTN
Stage II HTN
Resistant Hypertension

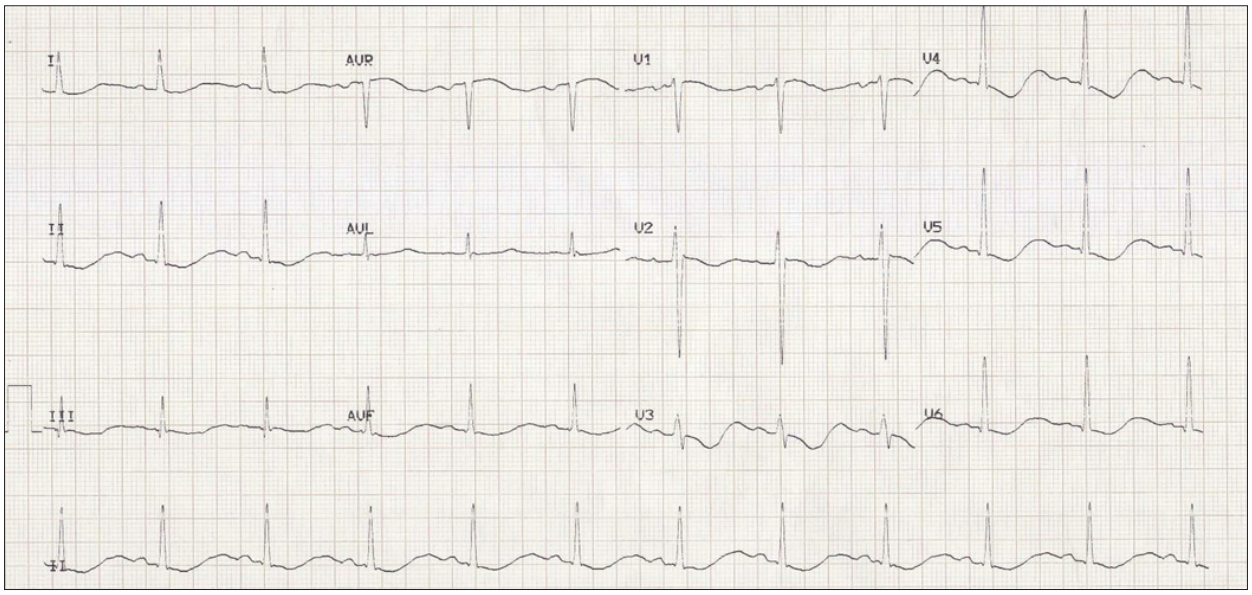


The sporadic causes of primary hyperaldosteronism are the most common cause of the disease- bilateral hyperplasia of both adrenal glands is the cause in 60-70% of the sporadic cases of the disease and the unilateral aldosterone producing adenomas is accounting for 30-40% of the sporadic causes of the disease. Much less common cause of sporadic primary hyperaldosteronism are the adrenal carcinomas producing aldosterone or unilateral adrenal hyperplasia. There are familial causes of primary hyperaldosteronism as well which are very rare/2/.

The Endocrine Society recommends primary aldosterone screening for people who meet one of the following criteria/1/

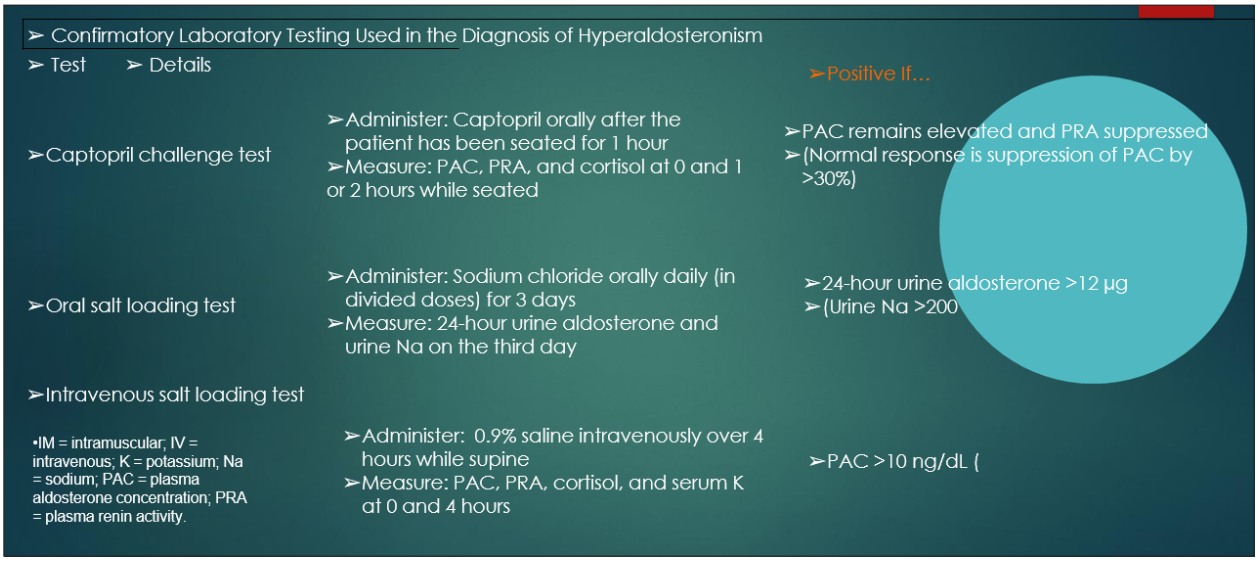
- Those who have sustained blood pressure above 150/100 in three separate measurements taken on different days;
- People who have hypertension resistant to three conventional antihypertensive drugs;
- People whose hypertension is controlled with four or more medications;
- People with hypertension and low levels of potassium in the blood;
- Those who have hypertension and a mass on the adrenal gland called an adrenal incidentaloma;
- People with both hypertension and sleep apnea;
- People with hypertension and a family history of early-onset hypertension or stroke before age 40; and
- All hypertensive first-degree relatives of patients with primary aldosteronism.

EKG: hypokalemia



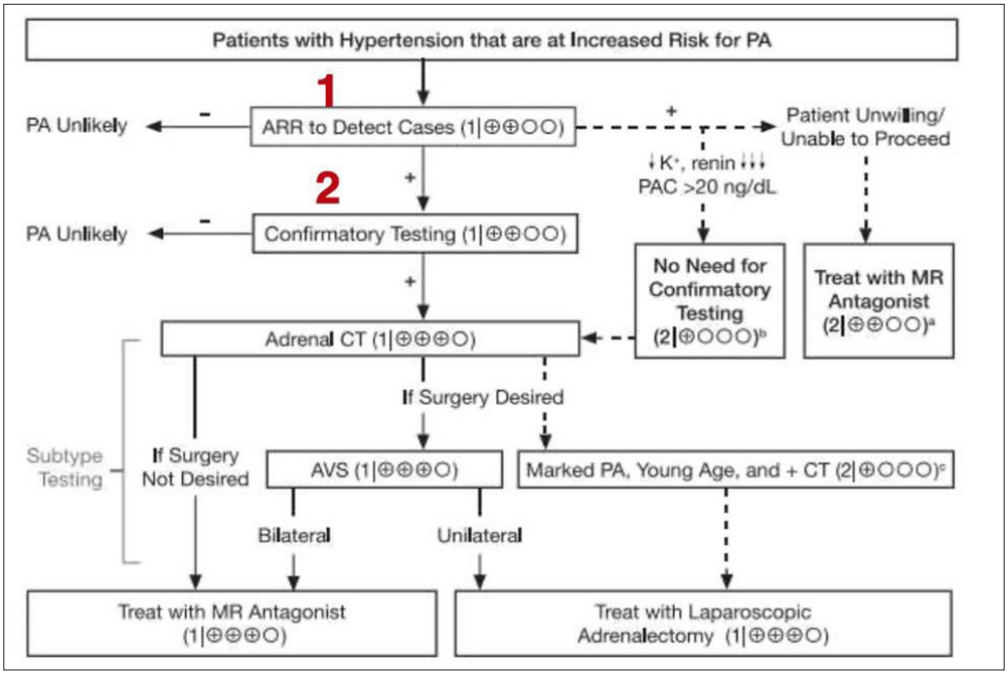
Screening tests for PA

- Simultaneous measurement of midmorning ambulatory plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in a volume replete, normokalemic patient
- Positive test: if PAC is frankly elevated (>/equal to 10 ng/dl), PRA is suppressed, and PAC/PRA ratio > 20/reff: <20)
- Some antihypertensive medication can affect measurements of PAC, PRA
- Stopping aldosterone antagonists for 4-6 wks prior to testing is recommended
- Diuretics should also be discontinued to assure euvolemia
- Verapamil, hydralazine, and a-blockers (doxazosin) can be substituted for BP control if necessary
- Referral to Endo is recommended when screening tests are abnormal



Other Tests After PA Confirmed Biochemically

- Once PA is confirmed biochemically, imaging localization with abdominal CT is indicated
- CT recommended over MRI due to similar efficacy and lower cost
- Adrenal hyperplasia and adenomas can be visualized; Adrenocortical CA can be ruled out
- Adrenal vein sampling (AVS) determines source of aldosterone secretion when imaging is unrevealing and to confirm lateralization which is especially important if the age of the patient is 35 or above- there might be unilateral/bilateral adrenal hyperplasia and nonfunctioning adrenal incidentalomas of the adrenal gland which increase with age



Treatment

- Goals: improve BP, normalize serum potassium, reduce plasma aldosterone
- If PA is due to aldosterone-producing adenoma or unilateral adrenal hyperplasia:
- Treatment of choice: Laparoscopic adrenalectomy
- HTN improves in majority of patients , but is cured in 40% with surgery. Persistent HTN is due to essential HTN or Vascular changes due to prior HTH. Usually resolution of HTN happens in patient with one or fewer first degree relatives with HTN and in patients with short duration of the disease and on fewer than 3- AHT medications. F/o Potassium level every week post operation because of transient reduction of aldosterone in the remaining adrenal gland due to chronic suppression. Also serum creatinine can increase , because hyperaldosteronism is high filtrate state. Needs to be monitored. Renin also improves to nl post operation. If hyperkalemia develops resistant to treatment short term MC needed rarely.
- If PA is due to bilateral adrenal hyperplasia or those with unilateral hyperplasia who are not surgical candidates:
- Treatment of choice: mineralocorticoid receptor antagonist (Spironolactone or Eplerenone)
- Amiloride is 2nd-line therapy because of lower efficacy
- Side effects of Spironolactone- dose dependent Gynecomastia and ED in men and menstrual dysfunction in females

Learning Objectives

Primary aldosteronism is a common syndrome that manifests across a broad severity spectrum from mild-to-severe and is under-diagnosed.

The primary aldosteronism syndrome contributes to idiopathic hypertension, and cardiovascular and kidney disease that can be prevented by available targeted therapies.

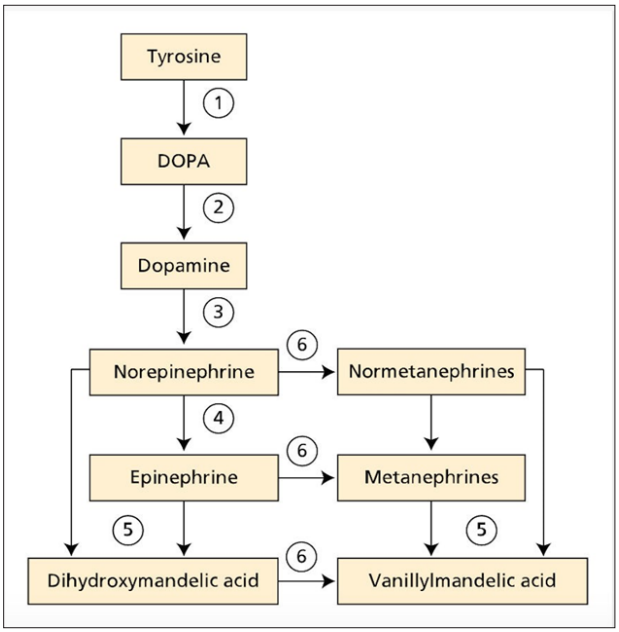
Screen more! Don't hesitate, Re-calibrate! A pragmatic diagnostic approach can maximize sensitivity and improve the detection (or empiric treatment) of primary aldosteronism

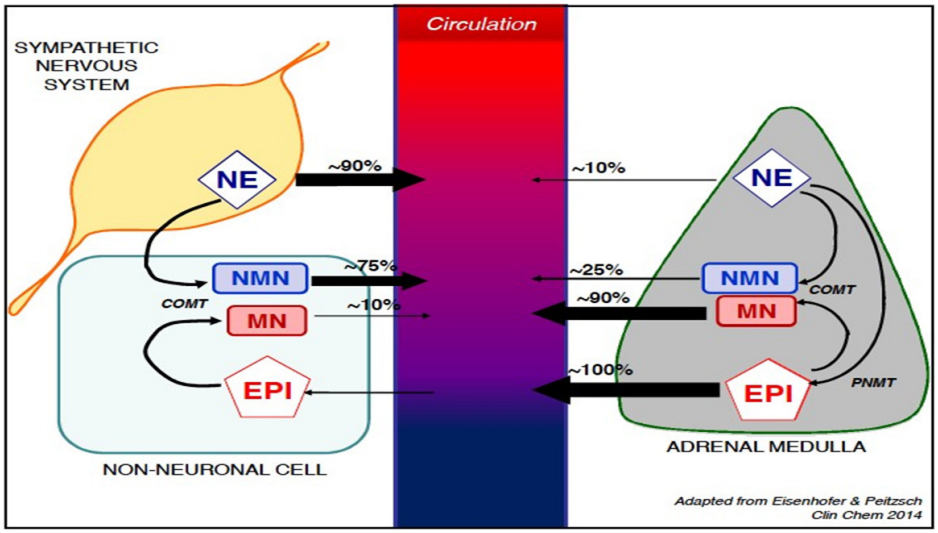
Pheochromocytoma and Paraganglioma

- Paraganglioma and Pheochromocytoma are tumors composed of chromaffin cells.
- 80% are intra-adrenal (pheochromocytoma); the rest come from extra-adrenal sympathetic or parasympathetic ganglia. The abdomen is the most common location of extra-adrenal sympathetic paraganglioma. Sympathetic paraganglioma synthesize norepinephrine, Dopamine and L Dopa , but not Epinephrine!
- Parasympathetic paraganglioma are usually found in the head and neck and are non functional
- Pheochromocytoma synthesize Norepinephrine, Dopamine and are the only one which synthesize EPINEPHRINE!

Catecholamine Metabolism

- Catecholamine hormones are produced in the adrenal medulla and sympathetic ganglia.
- The pathways of synthesis and degradation are shown.
- Excessive catecholamine secretion can occur with pheochromocytomas and paragangliomas.





Catecholamine's and their metabolites

Epinephrine and Norepinephrine have short half life and are released in pulses while their metabolites Metanephrine and normetanephrine called Metanephrines have long half life, are more stable and this is why we measured them in the blood.

Epidemiology

- Pheochromocytomas are rare tumors, occurring in 0.5% of hypertensive individuals and the patients may be completely asymptomatic.
- Approximately 10% of pheochromocytomas are discovered incidentally.
- Pheochromocytomas occur less frequently in African Americans. Peak incidence is from the third to the fifth decade of life. About 17% of pheochromocytomas and 20-50% of paragangliomas are malignant, but this number is changing upward!

Etiology

- 40% or more of pheochromocytomas and paragangliomas occur as part of a genetic disorder.
- Pheochromocytomas are seen with multiple endocrine neoplasia (MEN) syndromes:
- MEN Type 2A (along with medullary thyroid carcinoma and parathyroid hyperplasia)-RET gene
- MEN Type 2B (along with medullary thyroid carcinoma, mucosal neuroma, gastrointestinal ganglioneuroma, and Marfnoid body habitus)-RET gene
- Pheochromocytomas is also seen in Neurofibromatosis type 1, and von Hippel-Lindau syndrome (VHL)
- Paragangliomas and less frequently pheochromocytomas can occur as a part of familial paraganglioma syndrome mutations, some of which are associated with high rates of malignancy.
- In both disorders genetic testing needs to be done to the patient and first degree relatieves. Surveilance after treatment-if there is genetic mutation/or high risk features follow up with MRI every 1-2 years , catecholamines yearly and PE yearly

Pathophysiology/Clinical Presentation

- Most pheochromocytomas secrete norepinephrine and epinephrine , which results in episodic or sustained hypertension.
- Orthostatic hypotension is also seen, most likely due to low plasma volume. The excess catecholamine's have natriuretic effect and that way lead to decrease in plasma volume. Occurs more often if the tumor synthesizes mostly adrenaline- Pheochromocytoma.
- Classic pheochromocytoma triad of symptoms includes diaphoresis, headache, and tachycardia in 50% of patient10-15% of patients are normotensive.
- Other common symptoms include tremor, palpitations, pallor, sweating weight loss, abdominal pain, blurred vision, polyuria and anxiety. Rarely, patient present with acute MI, cardiomyopathy or CVA
- Less common features include papilledema and DM
- 17% of pheochromocytoma and 20-50% of paraganglioma are malignant, but this number is increasing

Pheochromocytoma and Praganglioma are associated with the following

- Increased risk of cardiovascular diseases and cardiovascular symptoms
- Increased risk of Psychiatric symptoms
- Decreased quality of life
- Increased risk of malignancy
- Genetic associations
- Increased risk of glycemic dysregulations among others.

When to suspect Pheochromocytoma and Paraganglioma?

1. Patients who have paroxysms/spells/ of increment of the blood pressure associated with tremor, palpitations, pallor, anxiety, headache, sweating etc.
2. Provocation of those paroxysms by beta- blockers, Sympathomimetic' s, MAO -inhibitors, SSRI's, Glucocorticoids, opioids or anesthesia, surgery or angiography
3. Incidentally noticed adrenal masses especially those with density > 10 HU
4. Known or suspected hereditary predisposition for Paraganglioma/ Pheochromocytoma associated syndromes-MEN2, NF-1,VHL etc.
5. Known personal history/FH of Pheochromocytoma/ Paraganglioma
6. HTN >140/90 on 3- drug therapy
7. Idiopathic cardiomyopathy
8. HTN with onset age onset <20
9. Paraganglioma

Diagnosis of Pheochromocytoma and Paraganglioma

- Should always start with clinical likelihood - can be high pre test probability or moderate to low
- Consider factors that might lead to false positive tests-
- Everything which increases the sympathetic nerve system tone- stress, critical illness, even non supine posture increases the plasma metanephrines
- Kidney diseases- because metanephrine's and catecholamine's are excreted by the kidneys
- Medications and drugs-MAO-inhibitors, cocaine, TCA, SSRI/SNRI, beta- blockers, infusions of Dopamine, epinephrine, norepinephrine, L Dopa etc.
- Suggested measurement of the plasma and urine metanephrine's and urine catecholamine's using liquid chromatography mass spectrometry- /LCMS/the most accurate test for measuring the metanephrines

Diagnosis

Diagnosis is based on the clinical likelihood of the disease and on confirmation of excessive secretion of catecholamines or their metabolites (metanephrines), measured in plasma or urine.

Sensitivity of plasma fractionated metanephrines is 96-100%, however specificity is 85-89%, so it will exclude Pheochromocytoma when negative, but if positive need further testing to confirm diagnosis unless >2-4 times upper limit of normal. Usually to avoid overlapping with medications/

illnesses etc. which may elevate catecholamine's marginally we look for elevations which are more then 2-4 fold above upper limits/ULN/ of normal suggesting of catecholamine producing pheochromocytoma or paraganglioma! Make sure that while checking plasma fractionated metanephrines the patient has been supine for 15-30 minutes with canula in the vein for 30- minutes before the blood is checked!

Diagnosis of pheochromocytomas and paragangliomas- (contunued)

24-hour urine fractionated metanephrines and catecholamines are 91% sensitive and 98% specific. Again to avoid overlapping with medications/ illnesses etc. which may elevate catecholamine's marginally we look for elevation which is more then 2-4 fold above upper limits of normal suggesting of catecholamine producing pheochromocytoma or paraganglioma!

Due to low frequency of false positives, 24-hour urine test are preferred when pre-test probability of disease is low (as with adrenal mass without typical radiographic appearance).

Plasma free metanephrines is preferred when clinical suspicion is higher (known hereditary syndromes).

CT or MRI of abdomen is preferred initial test in critically ill hospitalized patient because biochemical testing cannot be reliably interpreted in this setting.

At least 24 hours before testing, and preferably 2- weeks before testing discontinue medications and other substances which may falsely elevate levels of plasma and urine catecholamines or metanephrines.

Discontinue SNRIs (Venlafaxine) for about 2 weeks prior to testing to avoid false positive results.

Substances Associated with False-Positive Biochemical Testing for Pheochromocytoma	
Drug Class	Medication/Substance
Analgesics	Acetaminophen
Antiemetics	Prochlorperazine
Antihypertensives	Phenoxybenzamine[a]
Psychiatric medications	Antipsychotics Buspirone, SNRIs Monoamine oxidase inhibitors Tricyclic antidepressants[a]
Stimulants	Amphetamines, Methylphenidate Cocaine Caffeine
Other agents	Levodopa Decongestants (pseudoephedrine) Reserpine
Withdrawal	Clonidine Ethanol Illicit drugs

[a]Most likely to cause false-positive results.

Diagnosis of Pheochromocytoma and Paraganglioma c/o

Start with clinical Pre Test Probability

High clinical likelihood - Consider causes of False positive results and if they are low proceed with testing of plasma fractionated metanephrines and or 24- hour urine fractionated metanephrines and catecholamine's. If they are increased more then 2-4 times – usually 3 or more times NL we have biochemical confirmation of the diagnosis and proceed with abdominal CT or MRI and if there is a tumor proceed with surgery after initially controlling the BP with alfa- antagonists If abdominal CT /MRI is negative consider whole body MRI/ PET - CT for extra abdominal source and if negative- reconsider the DX and the causes of False positive biochemical tests. If the biochemical tests are elevated but less then 2- times normal or just normal , but high clinical pre test probability - follow up the patient in the future and repeat the hormonal studies.

Moderate to low Clinical likelihood for the diagnosis- Consider causes of False positive results like drugs, medications etc . If no such discuss with the patient the consequences of checking the urine or plasma fractionated metanephrines and then if the patient is willing to proceed check plasma fractionated metanephrines and or urinary fractionated metanephrines and catecholamine's.

If the values are less then 2 times upper limit of normal/ULN/ the diagnosis has been excluded. If the values are above 2-3 times ULN consider the diagnosis and perform as described above CT/MRI abdomen and if negative whole body MRI/PET -CT for extra adrenal tumor.

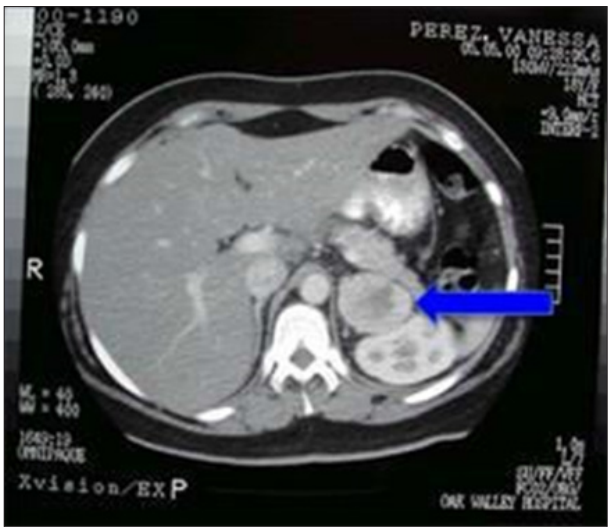
Diagnosis

After clinical and biochemical confirmation of Pheochromocytoma or paraganglioma the CT or MRI of abdomen and pelvis. Whole body PET -CT or MRI are used now if the CT/MRI of the abdomen are negative. Fluorine 18 fluorodeoxyglucose (FDG) PET – CT scan is the superior diagnostic test to identify metastatic disease.

[68 GA]-DOTATATE PET/CT is superior to other imaging modalities in Diagnosing metastatic Paraganglioma/ Pheochromocytoma Iodine 123 metaiodobenzylguanidine (MIBG) scan can be done, if multiple tumors, large pheochromocytomas >10 sm to detect metastatic dise, or malignant pheochromocytomas are suspected or iodine 131-labeled MIBG therapy is considered or if extra-adrenal location is suspected (paragangliomas) but majority of the centers now perform whole body PET- CT or MRI or in those situations or [68 GA]-DOTATATE PET/CT.

Pheochromocytoma on CT/MRI

- Variable size, heterogeneous enhancement, cystic areas, round, clear margins, can be bilateral.
- Hounsfield units >10 counts per unit, Contrast washout after 10 minutes less than 50% .
- Hyper-intense on T2 weighted images on MRI.



Pharmacological Treatment

Preoperative pharmacologic treatment is important for pheochromocytomas and paragangliomas to prevent massive release of catecholamines, which can lead to cardiovascular complications during surgery with increased incidence of stroke, MI, arrhythmia etc. Also in post operative period hypotension needs to be avoided -the excess catecholamine's have natriuretic effect and this decreases the plasma volume and leads to volume contraction with resultant postoperative hypotension . The alfa blockers also might lead to postoperative hypotension.

Alpha-adreno receptors are blocked first, usually with phenoxybenzamine for 10-14 days. CCBs and selective alpha1-blockers (terazosin/doxazosin) are also commonly used and can CCB be added treatment in large pheochromocytoma with high hormonal secretion. Side effect- nasal congestion, fatigue, dizziness.

Goal of BP < 130/80 mmHg seated and > 90 mmHg (systolic) standing.

Beta-adrenoreceptor blockers (metoprolol/propranolol) are ONLY added after alpha-blockers to treat reflex tachycardia and are especially helpful in patients with cardiac diseases, arrhythmia etc. Make sure first that the patient is not tachycardic because volume depleted.

Goal of HR of 60 to 70/min seated and 70 to 80/min standing. Starting beta-blocker before alpha-blocker can increase risk of hypertensive crisis due to unopposed alpha- receptor stimulation.

Rarely Metyrosin is added to the Phenoxybenzamine - inhibits tyrosine hydroxylase and that way decreases the cateholamine biosynthesis for large pheochromocytomas with high hormonal secretion

Surgical Treatment

Following pharmacologic treatment, due to fewer surgical complications and shorter postoperative hospital stays, laparoscopic adrenalectomy is preferred for removal of pheochromocytomas, except when the tumor is large- more than 6 sm or malignant tumors. Always make sure that the very experienced surgeon with this type of procedure has been selected! Pathology of the tumor cannot be reliable to r/o malignant versus benign tumor.

- Large-volume IV saline for volume expansion needs to be given after surgery to prevent hypotension.
- Vasopressors (norepinephrine) are sometimes needed for BP control.
- F/o BS also closely

Screening and follow up every year by checking plasma or urine metanephrines and doing every 2- years MRI of the abdomen also is considered in patients after operation with genetic mutations or who are high risk , but do not have genetic mutations yet described- young patients, personal history of associated malignancies, malignant pheochromocytoma/ paraganglioma, Family history of related diseases – for example Von- Hippel –Lindau syndrome, or MEN 2 or Neurofibromatosis , bilateral pheochromocytomas etc. New genetic mutations are described associated with familial pheochromocytoma or paraganglioma every year- 15 new mutations have been described since 2000. Metastasis found 50- years after removal of the tumor.

Even in patients who are at no high risk for familial disease which likely have sporadic disease is advisable follow up with updated genetic testing based on new genetic mutations described every year!

Also the screening is advisable for first degree relatives without the disease , but with genetic mutations

Follow up

- Metastases have been reported up to 50 years after diagnosis.
- Managed with additional surgery, iodine 131- labeled MIBG therapy, chemotherapy, and/or radiotherapy.
- Cure is achieved only if all the disease can be resected.

Prognosis

- 5-year survival rate for people with nonmalignant pheochromocytomas is greater than 95%.
- 5-year survival rate is less than 50% in patients with malignant pheochromocytomas.
- Although pheochromocytomas are rare, making the diagnosis is critical because the malignancy rate is 17 % , and patients can be completely cured with surgical removal.

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