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Endocrine HTN

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Suspicion for secondary HTN-10% of patients with HTN

1. Onset less than age of 30
2. Abrupt worsening of well controlled before BP
3. Resistant HTN
4. Clinical features of secondary process
5. Presence of target organ damage out of proportion to severity of HTN
6. Familial syndromes with HTN- VHL, NF1,PA etc.
7. Adrenal nodule with HTN
8. HTN with flash pulmonary edema
9. HTN and low potassium
10. Diastolic HTN with onset >65
11. HTN with sleep apnea
12. Unexplained CMP
13. HTN with acid- base disturbances
14. HTN with FH of HTN less than age of 40 and or CVA etc.

We will concentrate on the endocrine causes and mostly on adrenal causes of HTN.

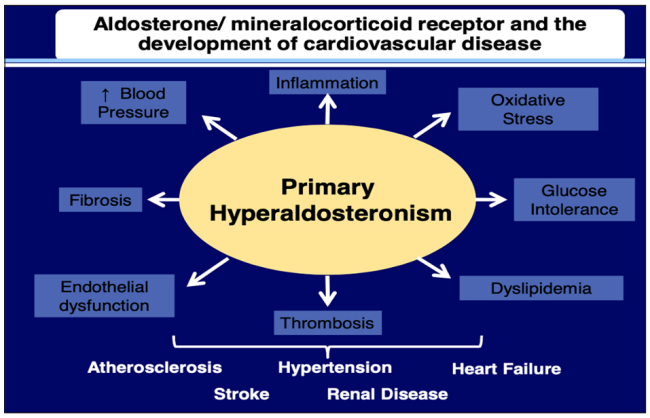
Secondary Causes of Hypertension and Diagnostic Testing	Diagnostic Testing
Underlying Cause	Serum creatinine; estimated glomerular filtration rate; urinalysis with microscopic examination; urine albumin-creatinine ratio; kidney ultrasonography
Kidney disease	Renal duplex Doppler ultrasonography; CT or MR angiography; renal artery angiography
Renovascular disease	Polysomnography
Obstructive sleep apnea	Plasma fractionated metanephrines; 24-hour urine metanephrines and catecholamines
Pheochromocytoma	Thyroid-stimulating hormone; free thyroxine
hypo- or hyperthyroidism	Intact parathyroid hormone; serum calcium and phosphorus
Primary hyperparathyroidism	Clinical diagnosis; family history; aldosterone and renin levels; electrolytes
Gordon syndrome (pseudohypoaldosteronism type II)	Blood pressure measurements in arms and legs; CT or MR angiography; transthoracic echocardiography
Aortic coarctation	
Conditions Associated with Hypokalemia	Diagnostic Testing

High aldosterone conditions: • Primary hyperaldosteronism: adrenal adenoma (rarely carcinoma or ectopic); bilateral adrenal hyperplasia • Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism; >50% normokalemic), type II, or type III • Secondary hyperaldosteronism: renal artery stenosis; renin-secreting tumor	Serum sodium and potassium concentrations; plasma aldosterone concentration/plasma renin activity ratio; saline suppression test; CT imaging; adrenal vein sampling; genetic testing
Cushing syndrome	Dexamethasone suppression test; 24-hour urine cortisol excretion; salivary cortisol
Congenital adrenal hyperplasia	Clinical diagnosis
Apparent mineralocorticoid excess	Clinical diagnosis; aldosterone and renin levels; electrolytes
Liddle syndrome	Clinical diagnosis; family history; aldosterone and renin levels; electrolytes

Primary Aldosteronism
Once a Zebra, Now a horse

What is Primary Aldosteronism?

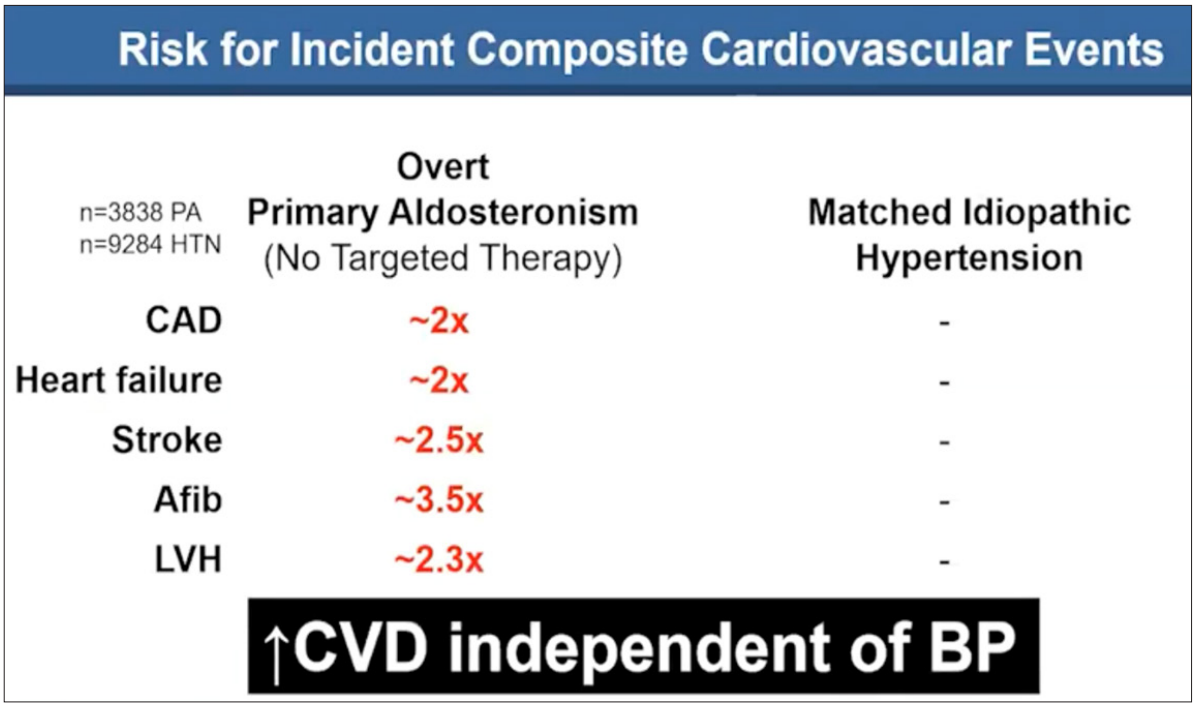
SYNDROME of Inappropriate, Relatively non-suppressible, Renin- independent aldosterone production that results in excessive activation of the renal-MR, vicious cycle of volume expansion => can increase BP, increases K^+/H^+ excretion, increases risk for CV disease independent of BP (extra-renal MR)

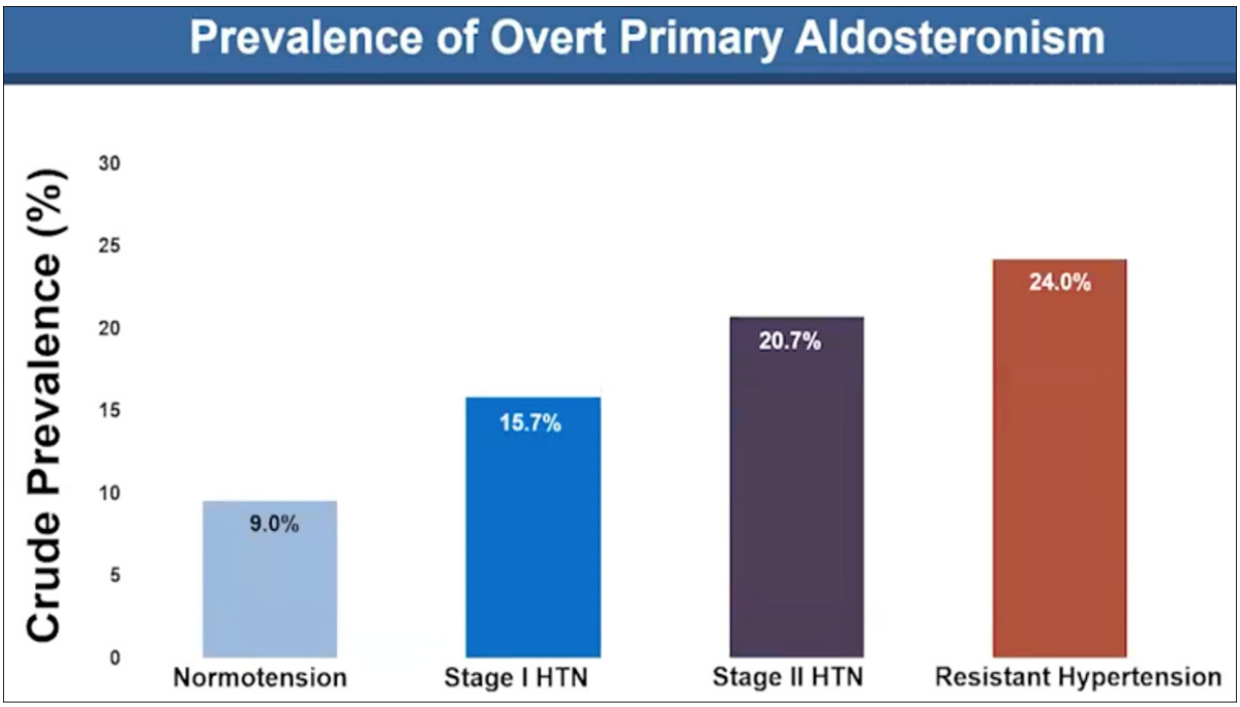


Clinical Manifestations

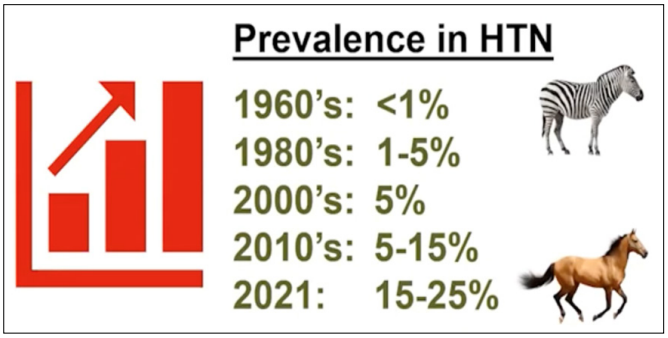
Reflect the severity and duration of the renin-independent aldosteronism BP and potassium are dependent features.

Hallmark Biochemical Diagnostics:
Suppression of Renin
Inappropriate/Dysregulated Production of Aldosterone





How Common is Primary Aldosteronism?

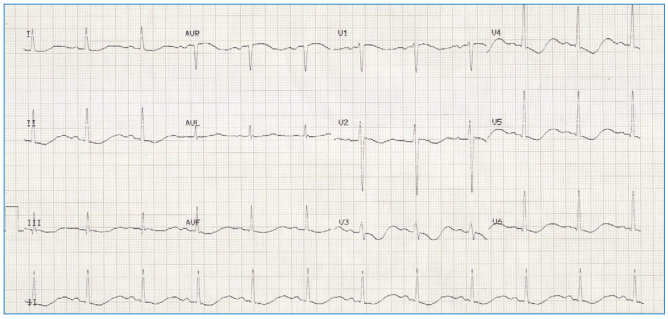


The sporadic causes of primary hyperaldosteronism are the most common cause of the disease- bilateral hyperplasia of both adrenal glands is the cause in 60-70% of the sporadic cases of the disease and the unilateral aldosterone producing adenomas is accounting for 30-40% of the sporadic causes of the 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



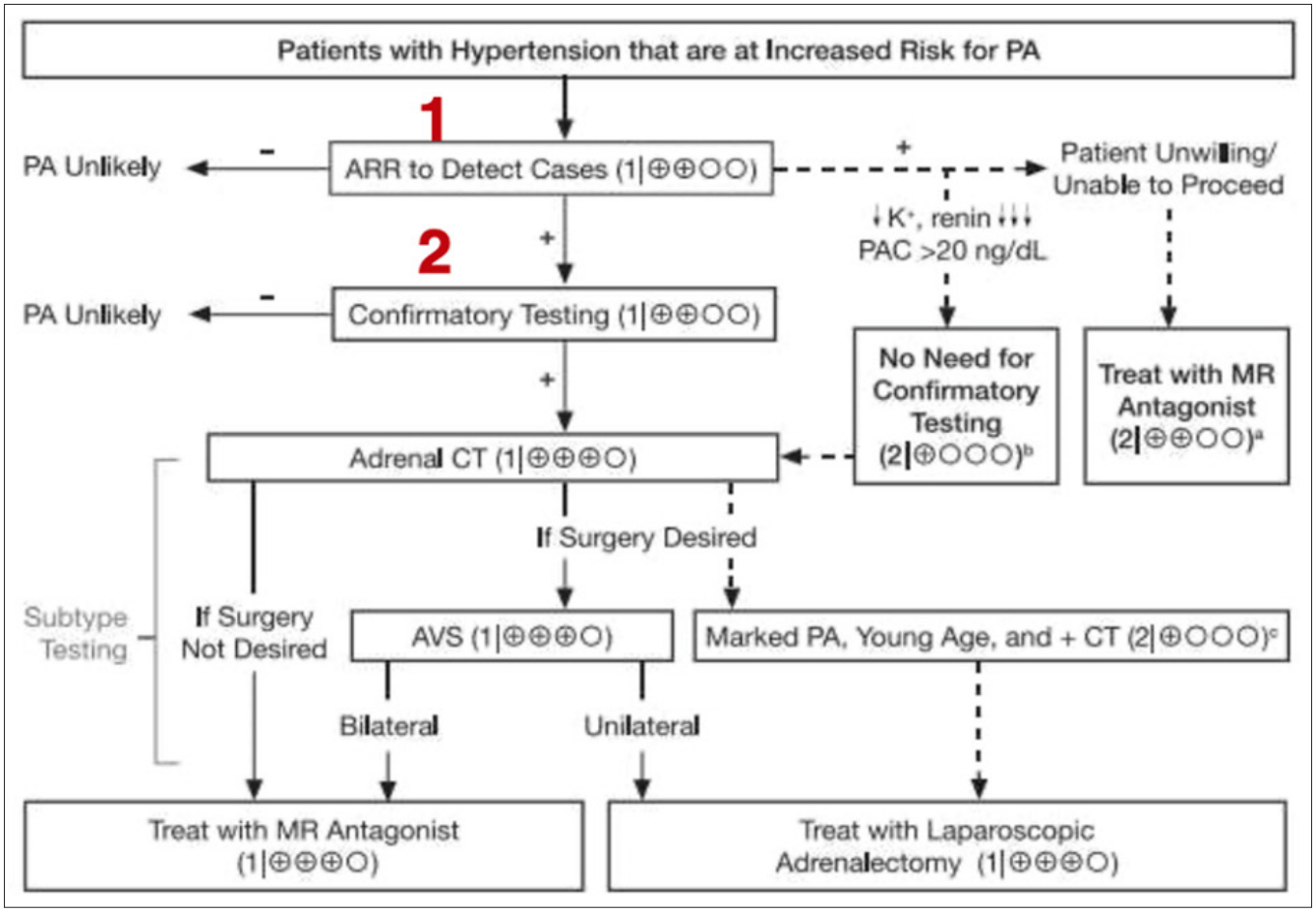
Primary Aldosteronism Screening Procedure: Stop Drugs?

- **Most Drugs OK for Screening**
  Most Drugs ↑PRA & Aldo (ß-Blockers ↓PRA) -
  If PRA is Suppressed, Screen is Valid
- **Up to 4 Wk:** Spironolactone, Eplerenone
  BUT STILL OK IF RENIN SUPPRESSED
- Best: $\acute{\alpha}_1$-Blocker + Verapamil
- Can Always Rescreen After Off Drugs

Primary Aldosteronism Screening Tests

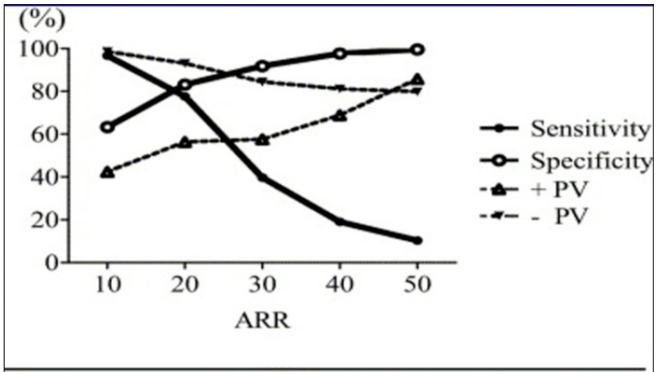
- **Random PAC/PRA or "ARR"**
  Ambulatory Test
  PAC >10 ng/dL AND PRA <1 ng/mL.h or
  DRC <10 pg/mL
  **PAC/PRA Dominated By Low PRA (+0)
- 24 h Urine Na, K

- Adequate Na Intake, NO K Supplements -K > 30-40 meq/d + Na > 100 meq/d
- Useful if Hypokalemic



Confirmatory Laboratory Testing Used in the Diagnosis of Hyperaldosteronism		
Test	Details	Positive If…
Captopril challenge test	**Administer:** Captopril orally after the patient has been seated for 1 hour **Measure:** PAC, PRA, and cortisol at 0 and 1 or 2 hours while seated	• PAC remains elevated and PRA suppressed • (Normal response is suppression of PAC by >30%)
Oral salt loading test	**Administer:** Sodium chloride orally daily (in divided doses) for 3 days **Measure:** 24-hour urine aldosterone and urine Na on the third day	• 24-hour urine aldosterone >12-14 µg • (Urine Na >200
Intravenous salt loading test	**Administer:** 0.9% saline intravenously over 4 hours while supine **Measure:** PAC, PRA, cortisol, and serum K at 0 and 4 hours	PAC >10 ng/dL
IM = intramuscular; IV = intravenous; K = potassium; Na = sodium; PAC = plasma aldosterone concentration; PRA = plasma renin activity.		

ARR Sensitivity & Specificity



Cut-off	Sensitivity	Specificity	+PV	-PV
ARR >20	**78**	**83**	**56**	**93**
ARR >50	10	99	86	80
ARR >20 and PAC >15	57	88	57	88 (%)

Nishizaka Am J Hypertens 2005 ; 18:805

Who has primary Aldo?
ARR Interpretation

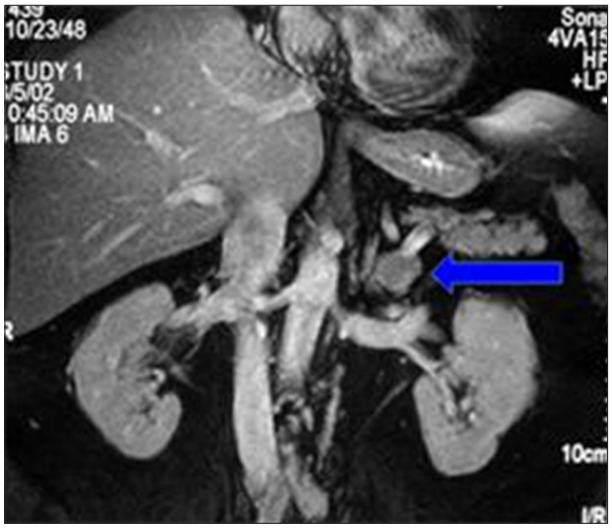
Aldo (ng/dL)	PRA (ng/mL/hr)	ARR	Serum Potassium (meq/L)	interpretation
6	3.2	2	4.4	Low ARR, not PA stop
3	0.1	30	4.0	Low Aldo,not PA stop
18	0.6	30	3.5	Positive screen for PA, go to confirmatory testing
11	0.8	15	2.9	Probably PA, supplement K, rescreen
38	2.0	19	4.2	Probably PA, stop meds and rescreen

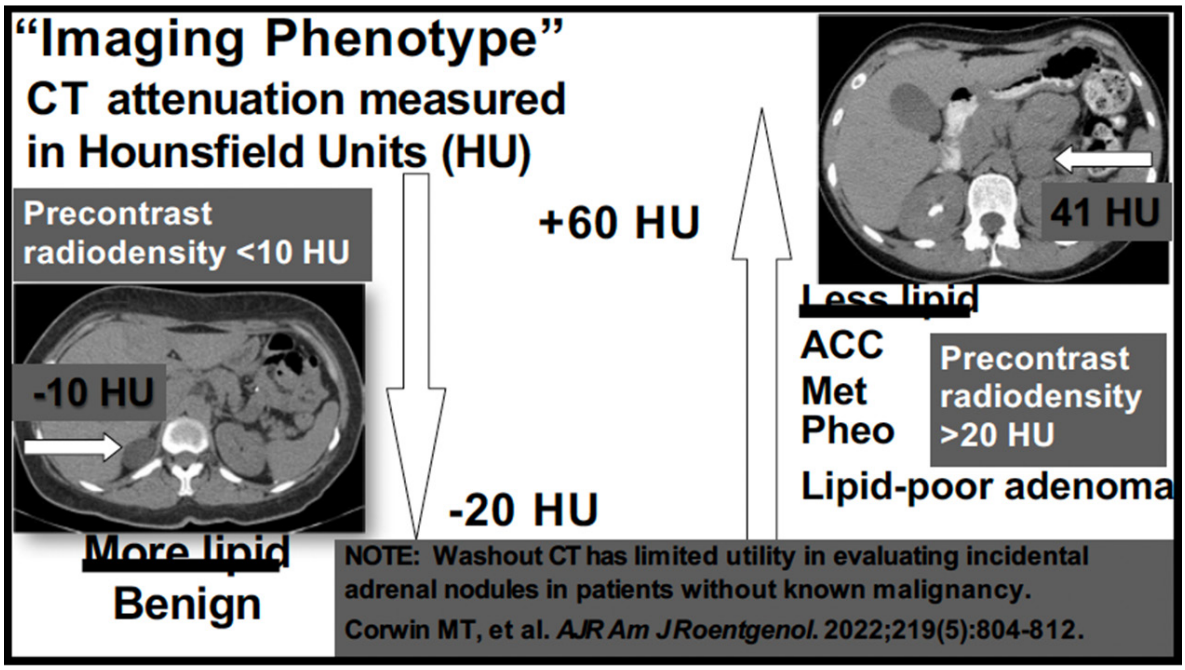
Primary Aldosteronism CT Scanning

- Too Sensitive: 5% Incidental Nodules
- Accuracy = 53%!!!!
- Incidental Nodules Are Common (~5%)
- Cannot Diagnose Bilateral Disease By CT Scan
  Cannot R/O Adenoma In Lumpy Gland(s)
- >1 cm Nodule IF The Contralateral Gland Is Clearly Normal in a <35 YO Patient

Adrenal adenoma

- CT without IV contrast enhancement should be the initial study
- If the adrenal mass is less than 10 Hounsfield units (HU), a diagnosis of adrenal adenoma can be made
- If the adrenal mass is more than 10 HU, CT with IV contrast material should follow, and the washout should be calculated
- Benign lesions typically demonstrate more than 50% washout within 10 minutes of administration of the iv contrast





Primary Aldosteronism

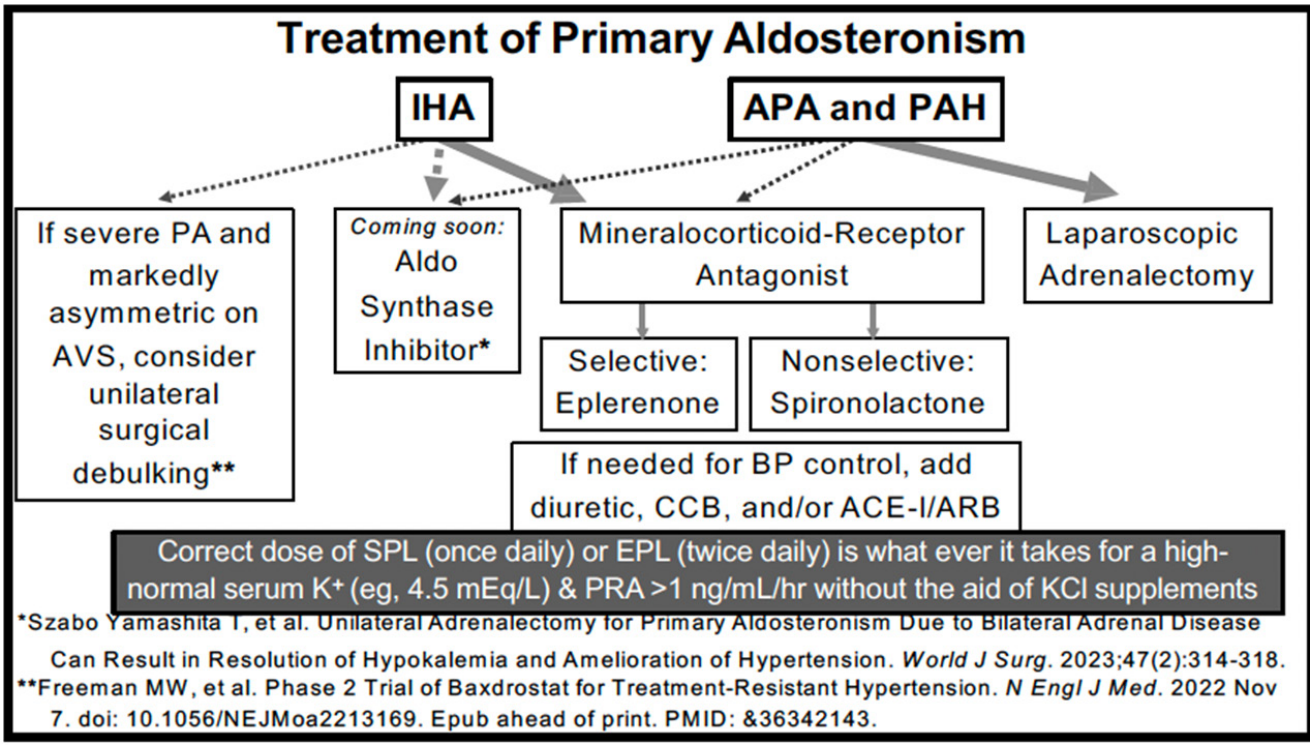
Adrenal Vein Sampling

- Plus or Minus Cosyntropin Bolus/Infusion
  Different Criteria for Access, Lateralization
- Sample R & L Adrenal Veins, IVC (PV)
- Sequential vs. Simultaneous Sampling
- 25% Failure to Access R Adrenal Vein
  Success Rate Varies Markedly with Centers

AVS Interpretation

- Mixed Venous Cortisol & Aldosterone
- RAV, LAV Cortisol = Selectivity Index (SI)
  ->2x IVC -Cosyntropin; >4x IVC +Cosyntropin
- A/C Gradients = Lateralization Index (LI)
  ->2 No Cosyntropin; >4 With Cosyntropin
  - Low Side < IVC = Contralateral Suppression
- Two Common Patterns (+Cosyntropin):

High AV	Low AV	IVC	Interpretation
40-50	0.5-1.5	1-5	Lateralized
2-4	2-4	1-2	Bilateral



Primary Aldosteronism

Treatment

- Surgery: Treatment Of Choice For APA
- Spironolactone 25-200 mg/d
  - Only Option For BHA, Aldo Tends To Rise
  - APAS Can Also Be Managed Medically
- Side Effects Limit Compliance For Males
- Eplerenone 50-200 mg QD-BID
  - Selective MR Antagonist

Pearls to Using MRAs

- Start Low Go Slowly: Spiro 12.5-25 mg/d
  - Chemistries in 2 Weeks, 1 Week if CKD Stage 2-4 - Do Not Up-Titrate for 4-6 Weeks
  - Double Dose & Iterate, Max ~400 mg/d
  - Goal: Normal BP & K, Non-Suppressed PRA Ideal - Consider Stopping Other Meds During Titration
  - Can Add Thiazide, Loop Diuretic For High K
  - Expect Rise in Cr; May Stop/Reduce Dose
- Switch to Eplerenone if Side Effects
  - Double Spiro Dose & Divide BID

Primary Aldosteronism

Surgical Success - PASO Study

- Hypokalemia Normalization >94%
- BP Improves 47%, Cure 37%, None 16%
- Predictors of BP Improvement
  - Younger Age, Lower BMI
  - Female Sex
  - Fewer BP Meds
  - Higher Aldosterone/Renin Ratio
  - Shorter Duration of HTN, No FH HTN

Monogenic Primary Aldo

Familial Hyperaldosteronism Type 1

- CYP11B2/CYP11B1 Fusion Gene; Aldo in ZF
- Hybrid Steroids: 18OH- & 18-oxo-Cortisol
- Cerebral Hemorrhage Common

Familial Hyperaldosteronism Type 2

- CLCN2 Gene

Familial Hyperaldosteronism Type 3

- KCNJ5 Mutations, +/- Massive Hyperplasia
- Familial Hyperaldosteronism Type 1
- CYP11B2/CYP11B1 Fusion Gene; Aldo in ZF
  - Hybrid Steroids: 18OH- & 18-oxo-Cortisol
  - Cerebral Hemorrhage Common
- Familial Hyperaldosteronism Type 2
  - CLCN2 Gene
- Familial Hyperaldosteronism Type 3
  - KCNJ5 Mutations, +/- Massive Hyperplasia
- Somatic Mutations in APA Tumors
  - KCNJ5, ATP2B3, ATP1A1, CACNA1D

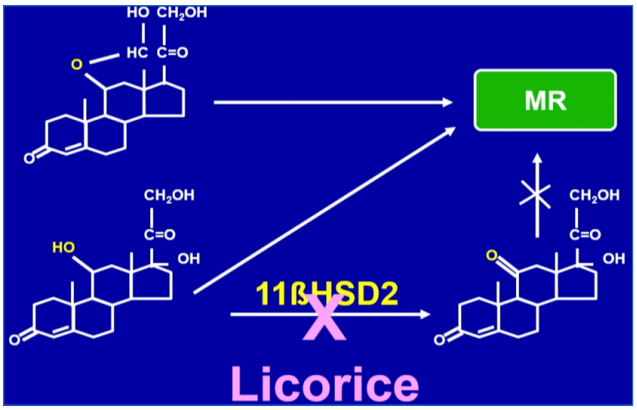
Mineralocorticoid HTN Differential Diagnosis

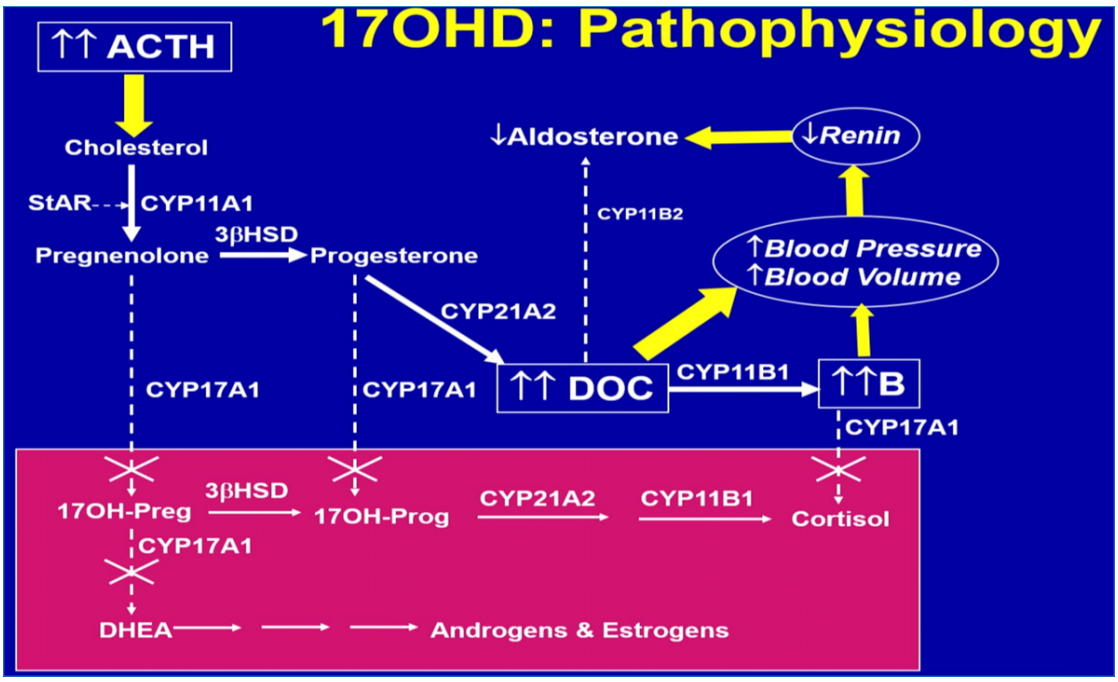
- Primary Hyperaldosteronism
  - APA, BHA, FHAS; Mixed Forms! Secondary Aldosteronism
- Cortisol
  - Cushing Syndrome
- AME: 11ßHSD2, Licorice; Urine Cortisol>Cortisone 11-Deoxycorticosterone (DOC)
  - Tumor, Drugs, 170HD, 110HD
- Liddle Syndrome

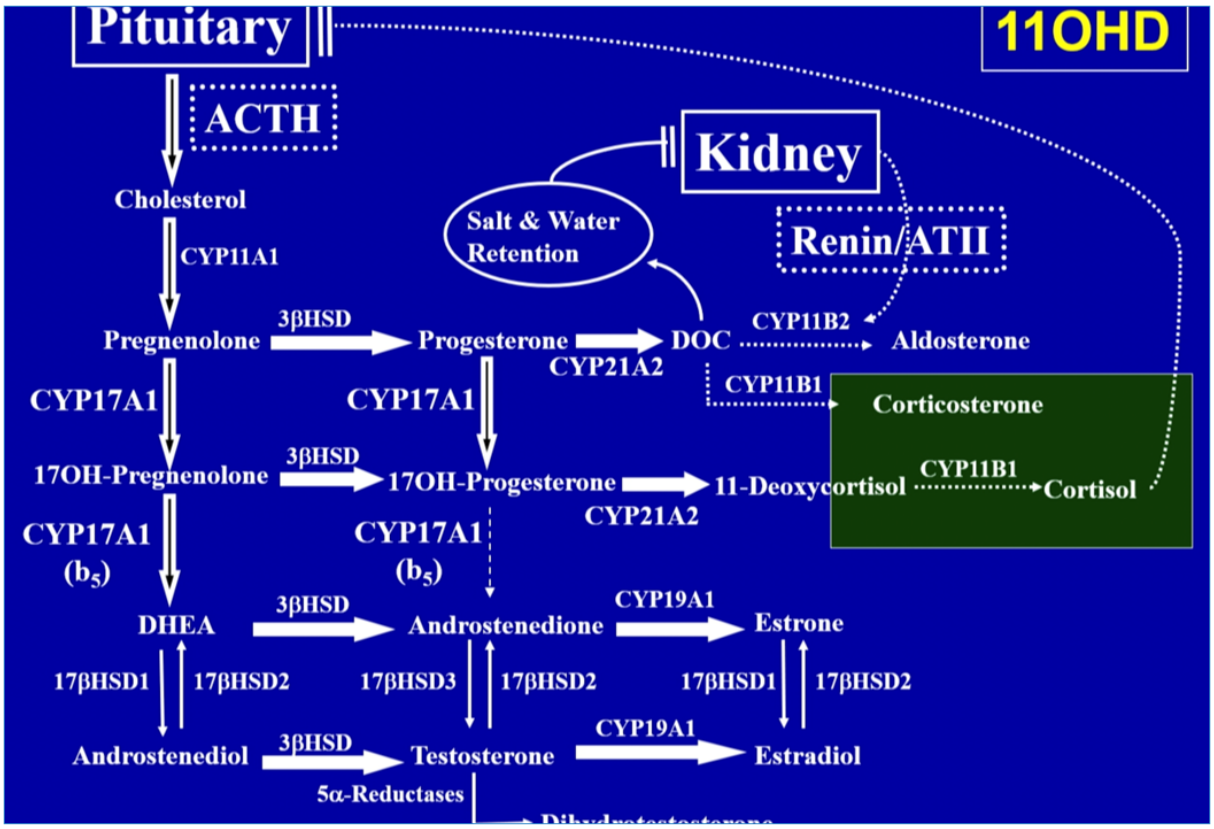
Causes of HTN and unprovoked hypokalemic alkalosis and low plasma renin and low aldosterone

1. DOC secreting tumors
2. 17-alfa-hydroxylase (CYP A1) deficiency
3. 11-beta-hydroxylase deficiency(CYP-B1)deficiency
4. Apparent mineralocorticoid excess(11-B-HSD2) deficiencyor Licorice
5. Liddle s-m
6. Activating variants of MC receptor
7. Severe hypercortisolism

Protecting MR from Glucocorticoids







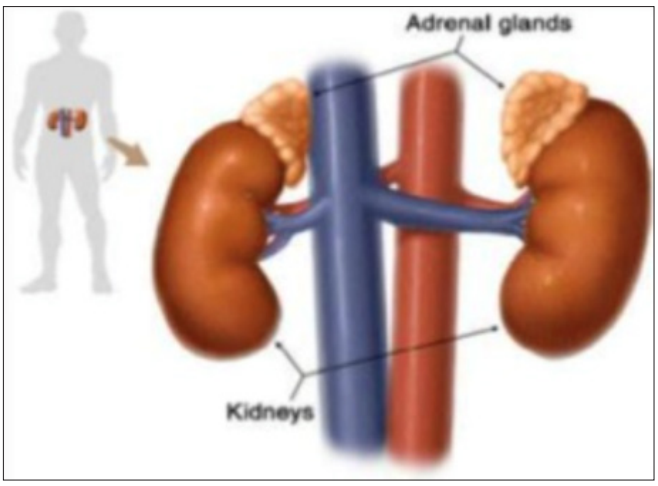
Endocrine HTN

Summary: Mineralocorticoids

- Know Who to Screen and When to Stop
- Must Confirm Non-suppressible Aldo
- Do Not Be Duped by CT Scans
- AVS for Most PA Cases Prior to Surgery
- Genetics of Mineralocorticoid Excess
- Do Not Forget Other Mineralocorticoids
- Spironolactone, Eplerenone, Etc Medical Rx

Secondary Hyperaldosteronism

Secondary Hyperaldosteronism is when the excess aldosterone is caused by something outside the adrenal gland and mimics the primary condition.



Symptoms of secondary hyperaldosteronism

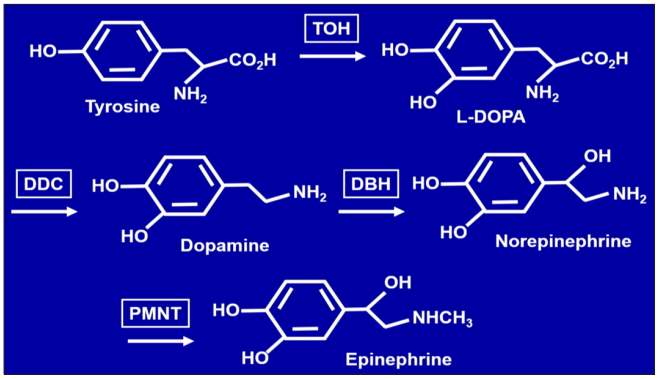
1. The patient might have HTN
2. Weakness, numbness, tingling, palsy due to low K , arrhythmias etc.
3. The patients might have edema- in patients with Cirrhosis, CHF, nephrotic syndrome.
4. Plasma Renin Activity and Plasma Aldosterone Concentration are increased.

Pheochromocytoma and Paraganglioma

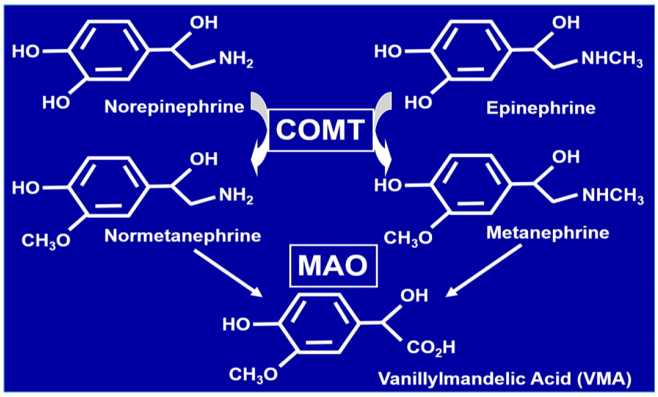
Background

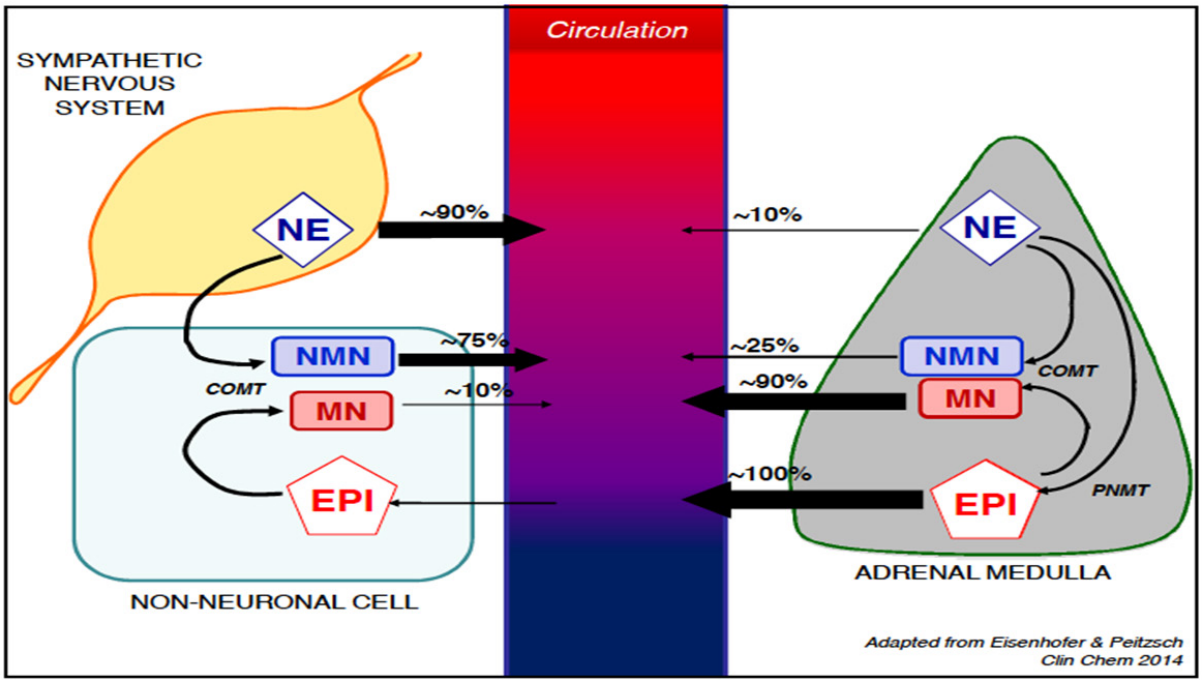
- Paraganglioma and Pheochromocytoma are tumors composed of chromaffin cells.
- 80% are intra-adrenal (pheochromocytoma); the rest come from extra-adrenal sympathetic or parasympathetic ganglia. The abdomen is the most common location of extra-adrenal sympathetic paraganglioma. Sympathetic paraganglioma 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 Biosyntheis



Catecholamine Catabolism





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.

Etiology

- 40% or more of pheochromocytomas and paragangliomas occur as part of a genetic disorder.
- Pheochromocytomas are seen with multiple endocrine neoplasia (MEN) syndromes:

1. MEN Type 2A (along with medullary thyroid carcinoma and parathyroid hyperplasia)-RET gene
2. 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-SDHB,D etc.
- 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.

Genetic Testing

- 40% of patients with pheo/PGL have disease-causing germline mutations
- Hereditary pheo/PGL tumors typically present at a younger age than sporadic neoplasms
- Genetic testing should be considered in and discussed with all patients-especially if a patient has one or more of the following:

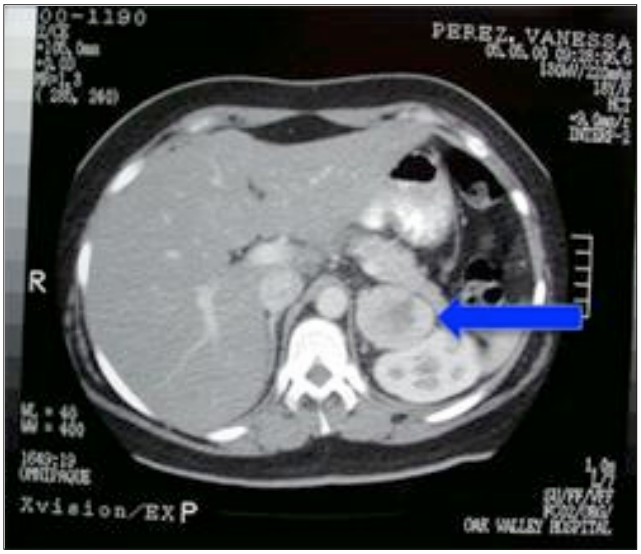
1. PGL
2. bilateral adrenal pheo
3. unilateral adrenal pheo & + FHx of pheo/PGL
4. unilateral adrenal pheo & young age (<60 y)
5. other clinical findings suggestive of one of the syndromic disorders

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 less than 50% of patient.
- 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.
- Mode of DX changed- 60% are discovered as adrenal incidentalomas. Less than 50% of patients have symptoms. When present- usually paroxysmal, but most of patients with HTN spells do not have the disease. Out of adrenal incidentalomas -2 % are pheochromocytomas
- Look for pressor response to anesthesia, angiography, Metoclopramide, High dose steroids-8 mg Dexamethasone, HTN at young age <30, familial syndromes-VHL,NF1,MEN2A,B, paraganglioma syndromes-SDHx, resistant HTN.
- Initial test for pheochromocytomas/paragangliomas- CT abdomen/pelvis. 95% are under the diaphragm.

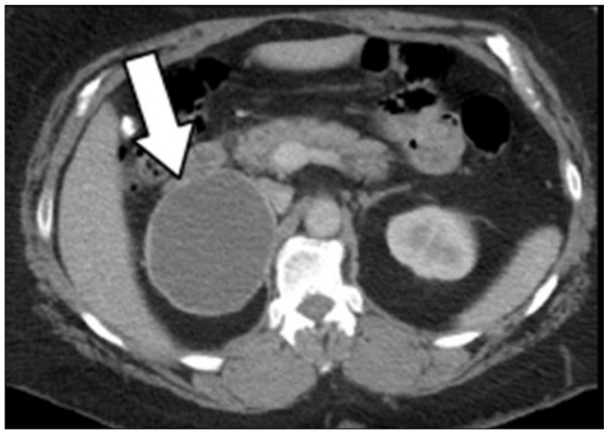
Pheochromocytoma on CT/MRI

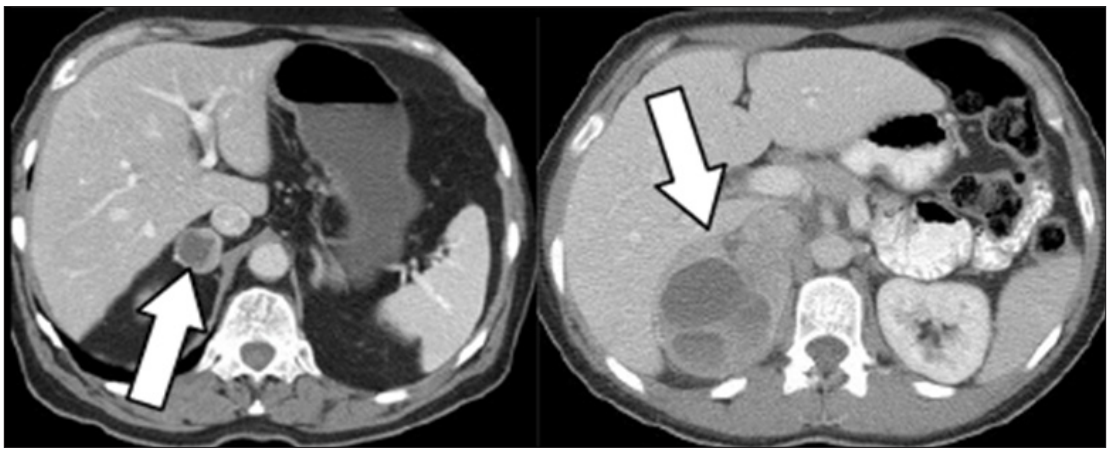
- Variable size, heterogeneous enhancement, cystic areas, round, clear margins, can be bilateral.
- Hounsfield units >10 counts per unit, Contrast washout after 10 minutes less than 50% .
- Hyper-intense on T2 weighted images on MRI.



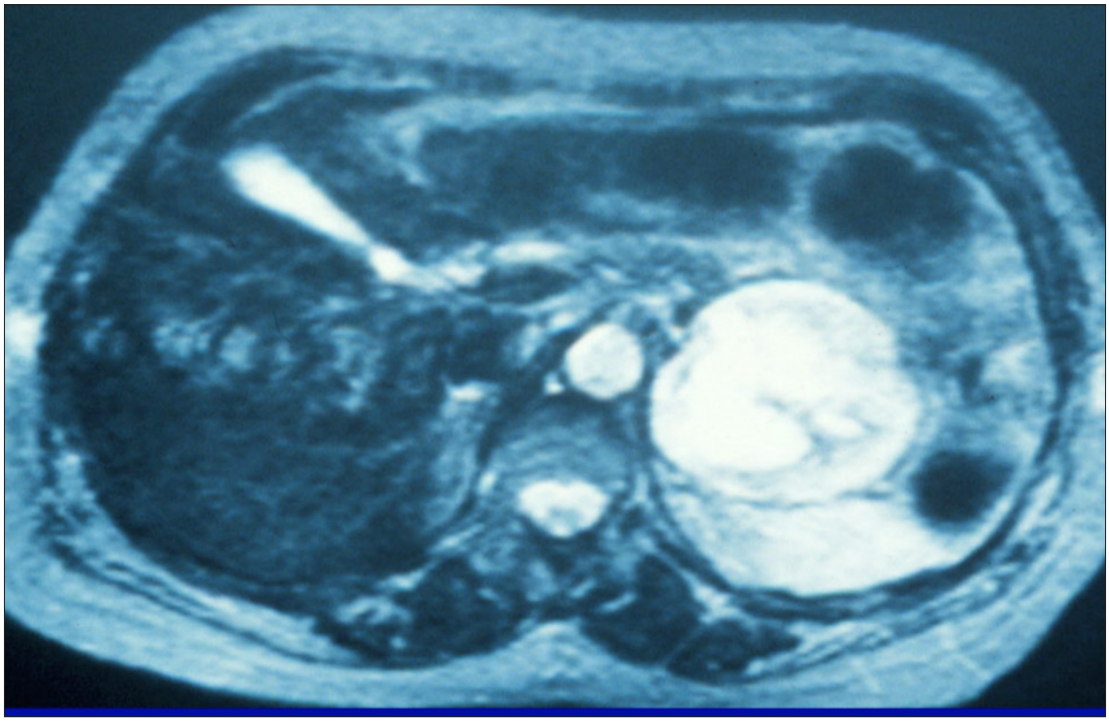
Pheo Imaging Phenotype

- Dense and vascular
- Inhomogeneous with cystic degenerative areas—BEWARE of the adrenal cyst!





Phoe : Hyperintense on T2 - MRI



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

Pheochromocytoma

Clinical Features

- Pressure: Sustained HTN + Spikes
- Pain: Throbbing HA, Chest Pain
- Perspiration: Heavy, Generalized
- Palpitations
- Pallor
- Other: Hyperglycemia, Weight Loss, Tremor, Orthostasis, Hypercalcemia, Fatty Liver, Cardiomyopathy
- Asymptomatic - Incidental Finding

Pheochromocytoma

The Pheo Paroxysm ("Spell")

- Throbbing HA & Chest Pain
- Drenching Sweat
- Pounding Tachycardia
- Extreme BP Elevation
- Pallor, All Lasting 10-60 Min
- NO Flush, Wheezing, Itching, Diarrhea, Dermatographia
- DDX: Menopause, OSA, Clonidine

- At least 24 hours before testing, Antihypertensives 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
Stimulants	Amphetamines, Methylphenidate Cocaine Caffeine
other agents	Levodopa Decongestants (pseudoephedrine) Reserpine
Withdrawal	Clonidine Ethanol Illicit drugs

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

Common Sense Tips on Diagnosis

Additional tips

- Fractionated plasma normetanephrine has a 15% false positive rate-combine that piece of information with the rarity of pheochromocytoma and you will find that 97% of patients with increased plasma pormetanephrine will NOT have a pheochromocytoma!*
- However, when plasma metanephrine is even mildly elevated take it seriously!

*Sawka AM, et al. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab. 2003;88:553-8.

Pheochromocytoma Screening Tests

- 24 h Urine Metanephrines
  - >2x Normal = 400 µg Metanephrine, 900 µg Normetanephrine
- Plasma Metanephrines: More False Positives
  - Seated 5 Min; Indwelling Catheter Best
  - NorMN >0.9 nM = 148 pg/mL or MN >0.5 nM = 57 pg/mL
  - Drugs to Avoid: TCAs, SSRIs, MAOIS, Phenoxybenzamine
- Grossly Positive Screen Sufficient
- Most Slightly Abnormal Screens Not Pheo
- Symptoms Correlate With Catecholamines
- Small Tumors Do Not Cause Symptoms (>3x Normal)

Common Sense Tips on Diagnosis

- Suppression testing with clonidine or provocative testing with glucagon, histamine, or metoclopramide are NEVER needed
- In a pt with spells, the degree of ↑ of fx mets & cats should be markedly abnormal-in other words, if a pheo is responsible for "classic pheochromocytoma spells", then the biochemical tests are ALWAYS unequivocally abnormal (eg, >5-fold above the ULN)

Pheochromocytoma

Plasma vs. Urine Metanephrines

- Plasma More Sensitive But Less Specific
  - Plasma Metanephrines = 99% Sens, 89% Spec
  - Urine Metanephrines = 76% Sens, 94% Spec
  - Urine Catechols = 83% Sens, 88% Spec
- High Suspicion, Presymptomatic Screen
  - MEN2, NF-1, VHL Kindreds
  - MEN2: Metanephrine Best
  - VHL: Norepinephrine, Normetanephrine Best
- AVOID: Glucagon, Metoclopramide, IV Glucocorticoids

Diagnosis of Pheochromocytoma and Paraganglioma c/o

- Start with clinical Pre Test Probability
- A. 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
- B. 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.

Localization(1)

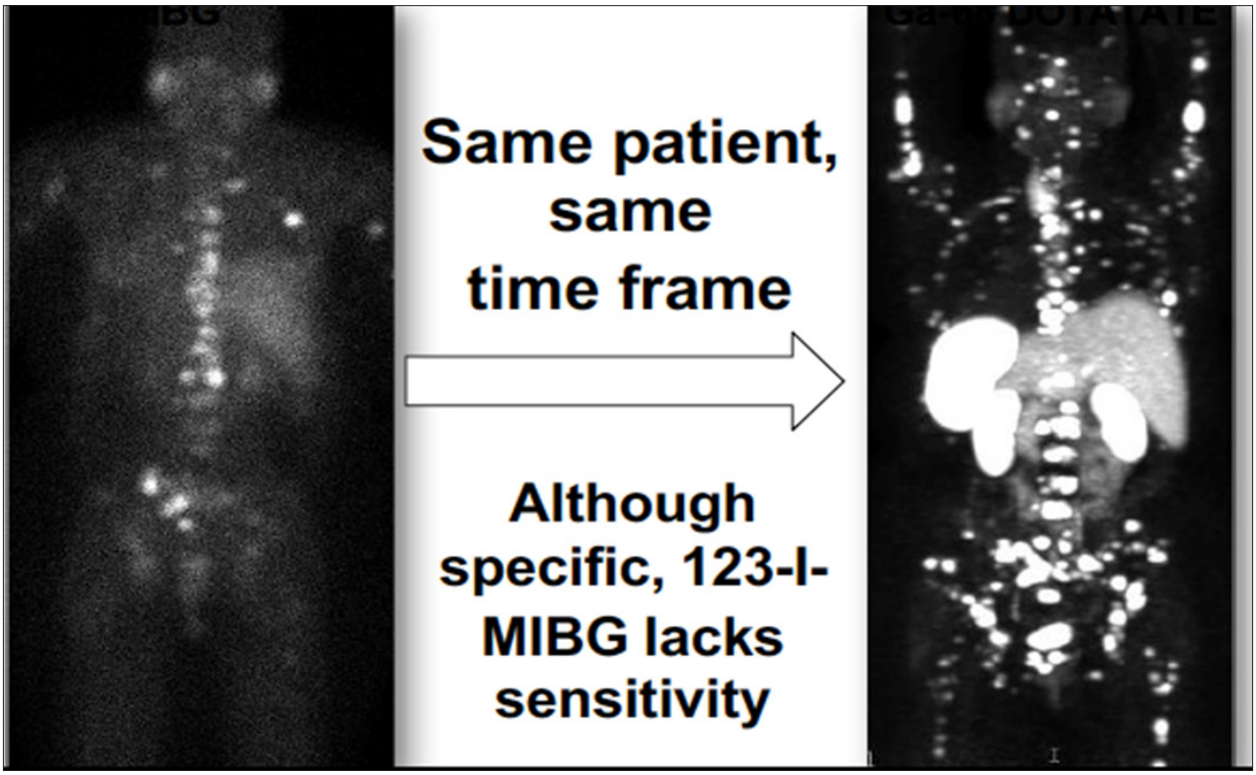
- We usually do not proceed with localization studies until biochemical studies have confirmed the dx of a catecholamine-secreting tumor
- Computer-assisted imaging of the adrenal glands abdomen with contrast-enhanced CT should be the first localization test (sensitivity, >95%; specificity, >65%)
- Approximately 85% of these tumors are found in the adrenal glands, and 95% are found in the abdomen and pelvis

Common Sense Tips on Localization

- The tumor can always be found in the symptomatic pt with pheo-the avg diameter is 4.5 cm. If you are having trouble localizing a pheo, it is usually because your pt does not have a pheo & you have ignored some of the biochemical dx tips
- MRI is over-rated
- EPI/metanephrine-predominant tumors will "always" be localized to the adrenal medulla
- NE/normetanephrine-predominant tumors may arise from the adrenal medulla or from sympathetic paraganglioma in the abd, pelvis, chest, or neck

Localization (2)

- Ga-68 DOTATATE PET CT or FDG-PET CT or 123-1- metaiodobenzylguanidine (MIBG) scintigraphy are indicated if abdominal imaging is neg or if you are looking for additional PGLS or metastatic disease
- If a typical (<8 cm) unilateral adrenal pheo is found on CT or MRI, nuclear imaging is superfluous and may even confuse the clinician
- If the adrenal pheo is >8-cm in diameter or if a PGL is found, then 68-Ga-DOTATATE PET, FDG-PET, or 123-I-MIBG scintigraphy are indicated because the pt has ↑ed risk of malignant disease or additional PGLS



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 < 120/80 mmHg seated and > 90 mmHg (systolic) standing. On the second or third day of Alfa blockage the patient is given high sodium diet- 5000mg/day. This degree of volume expansion might be contraindicated in some patients with CHF,CKD etc.
- 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. Usually the last 2-3 days before surgery we add them. Make sure first that the patient is not tachycardic because of volume depletion
- Goal of HR of 60 to 70/min seated and 70 to 80/min standing. Last dose of alfa/beta blockers is given the morning of surgery.
- 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!
- 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 . May decrease , because of high Insulin levels before the operation.
- Post operation 1-2 weeks check plasma/urine methanephrines. If nl –surgery is complete.
- If elevated – surgery is not complete because of 2nd primary lesion or occult metastasis.
- Screening and follow up every year by checking plasma or urine metanephrines for life. Increment means recurrent primary tumor in adrenal bed , metastasis or delayed appearing primary tumors.
- Follow up imaging is done if mets/cats become elevated, original tumor had minimal catecholamine excess or the patient has PPGL germline mutation.
- 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

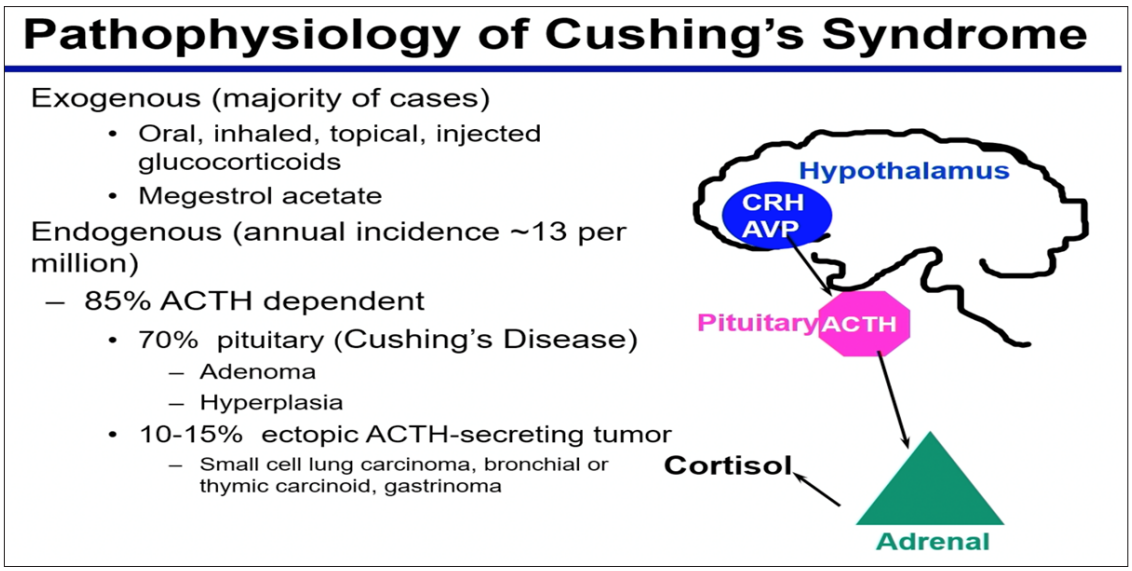
- 5-year survival rate for people with nonmalignant pheochromocytomas is greater than 95%.
- 5-year survival rate is less than 50% in patients with malignant pheochromocytomas.
- Although pheochromocytomas are rare, making the diagnosis is critical because the malignancy rate is 17 % , and patients can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

Epidemiology of Cushing Syndrome

Cushing Syndrome

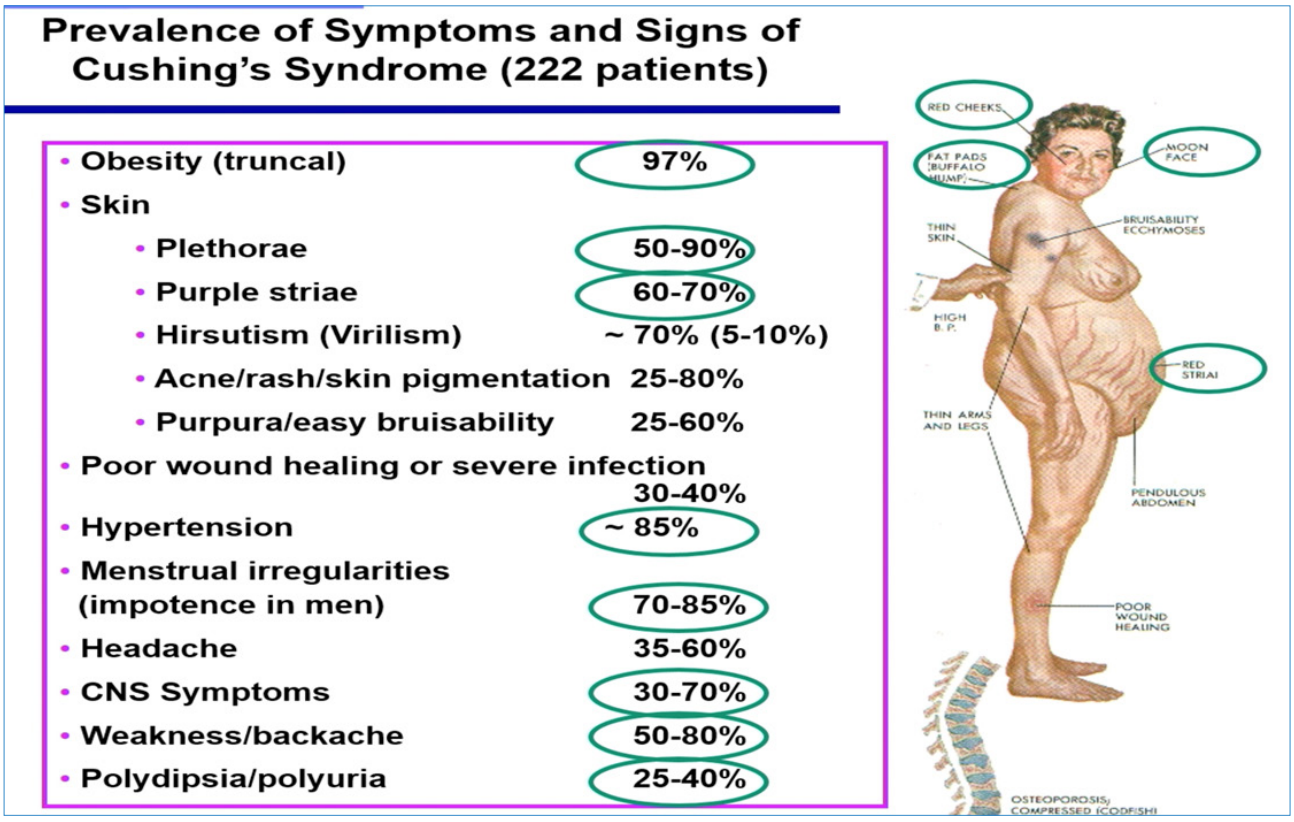
Cushing Disease

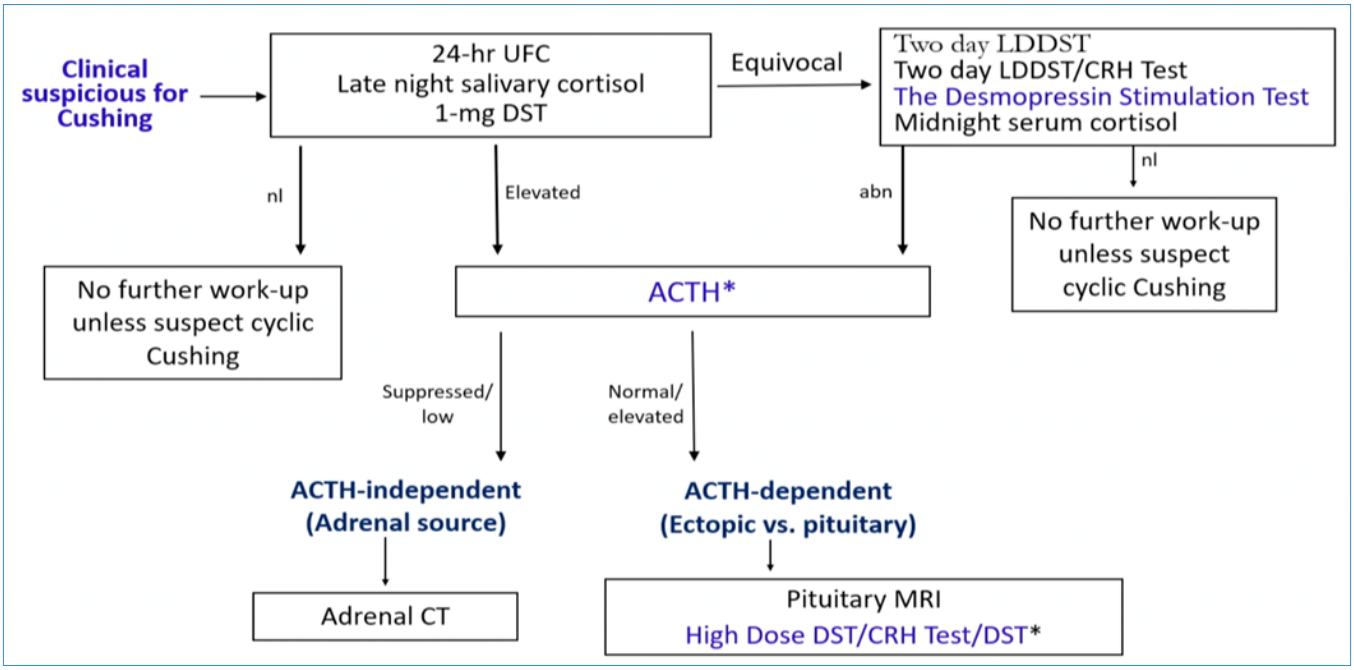
- Incidence of 1.2-2.4/million per year in two European population-based study
- Commercial claims database in the US: incidence 8/ million per year
- 3-8 times more common in women
- A prevalence as high as 5% among patients with uncontrolled diabetes or osteoporosis in tertiary centers has been reported*.
- Adrenal Cushing
- Incidence 0.8/million per year (adrenal adenoma & carcinoma)*
- Ectopic ACTH syndrome
- Small cell lung cancer makes ~50%



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





Role of DHEAS and adrenal incidentalomas:

1. If less than 40 mcg/dl- suspicion for SCS
2. If above 100 mcg/dl- unlikely SCS

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)

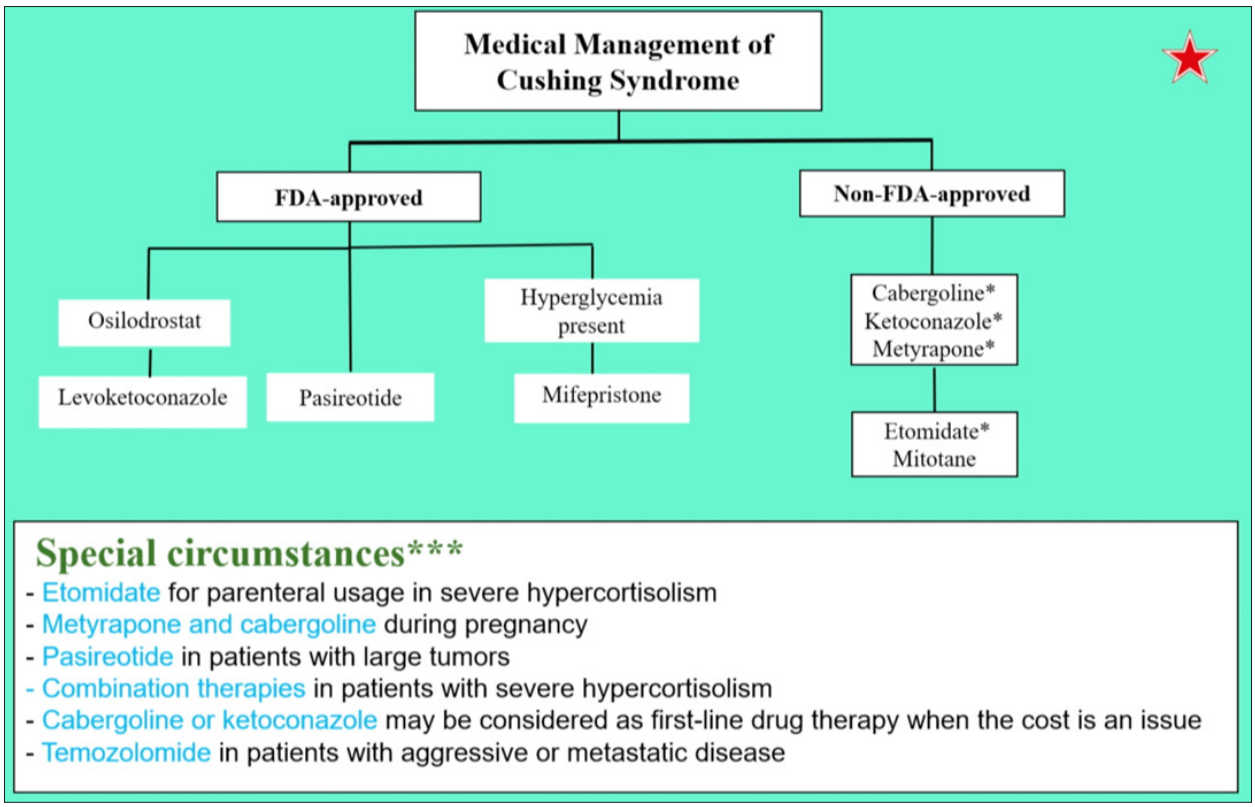
- 5-30% of patients with adrenal incidentalomas
- 1 mg DST is the preferred initial biochemical workup*
- A low ACTH and DEHAS levels support the diagnosis.

Post Unilateral Adrenalectomy Due to Adrenal Adenoma

- 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**

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

1. Recommendation is to normalize cortisol or its action at its receptors in order to eliminate symptoms
2. 1st line therapy- Surgery, for Adrenal Adenomas
3. 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 and monitor.
4. When surgery is delayed, treat with adrenal enzyme inhibitors (metyrapone, osilodrostat, ketoconazole, and etomidate in acute settings) or cortisol receptor antagonist mifepristone if hyperglycemia



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 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.

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