

Adrenal disorders

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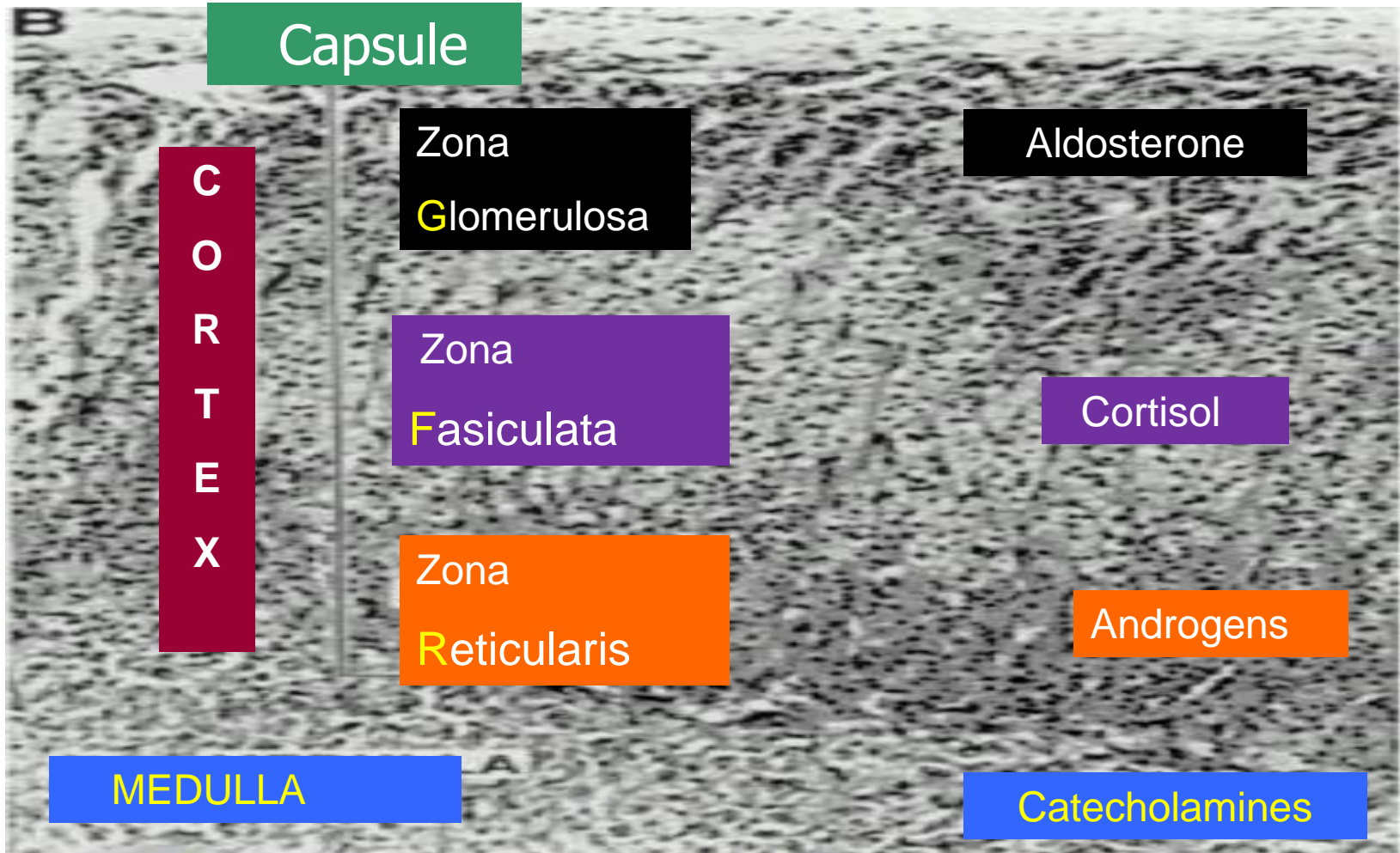
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Histology of the Adrenal gland



Adrenal insufficiency

When to suspect adrenal insufficiency?

- Symptoms not explained by other tests
- Presence of autoimmune diseases such as:
 - Type 1 DM
 - Hypothyroidism
 - Vitiligo
- Acutely ill patients with volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain

Manifestations of adrenal insufficiency

- Early stage:
 - Fatigue, dizziness
 - Anorexia, weight loss
 - Abdominal pain
 - Nausea, vomiting
 - Fever
 - Hyperpigmentation
 - Depression, anxiety
 - Loss of libido (women)

Adrenal crisis

- Late presentation of adrenal insufficiency:
 - Generalized weakness
 - Abdominal pain
 - Fever
 - Hypotension
 - Confusion
 - Coma

Laboratory findings in adrenal insufficiency

- Hyponatremia
- Hyperkalemia
- Metabolic acidosis
- Hypoglycemia
- Anemia
- Hypercalcemia

Causes of adrenal insufficiency

- **Primary**

- Disease of the adrenal gland. “Addison’s disease “
- Cortisol and mineralocorticoid deficiency

- **Secondary**

- Interference with ACTH (pituitary gland)
- Cortisol deficiency

- **Tertiary:**

- Interference with CRH (hypothalamus)
- Cortisol deficiency

Causes of primary adrenal insufficiency

- Autoimmune (most common)
- Destructive:
 - TB
 - Fungi
 - HIV
 - Metastasis, sepsis, emboli, infarction
 - Hemorrhage (anticoagulation, coagulopathy)

Causes of secondary adrenal insufficiency

- Part of hypopituitarism
- Isolated ACTH deficiency
- Autoimmune
- Traumatic brain injury

Causes of tertiary adrenal insufficiency

- Abrupt cessation of high-dose glucocorticoids:
 - They decrease CRH
- Cure of hypercortisolism (Cushing's syndrome):
 - After removal of a pituitary or non-pituitary ACTH-secreting or a cortisol-secreting adrenal tumor
 - The chronically high serum cortisol before surgery suppresses the hypothalamic-pituitary-adrenal axis
- Tumors, infiltrative diseases (sarcoidosis), cranial radiation

Diagnosis of adrenal insufficiency

- AM (8-9 am) cortisol < 3 mcg (83 nmol) highly suggests adrenal insufficiency:
 - ◆ Repeat to confirm
 - ◆ ACTH level (if available):
 - High = primary insufficiency
 - Normal or low = secondary insufficiency
- AM cortisol ≥ 18 mcg (497 nmol) is normal and no need for ACTH stimulation test
- AM cortisol > 3 & < 18 mcg: do ACTH stimulation test

Diagnosis of adrenal insufficiency

- ACTH (Cosyntropin, Synacthen) stimulation test:
 - ◆ Baseline serum cortisol
 - ◆ Give ACTH 250 micrograms IV bolus
 - ◆ Then check cortisol after 30 & 60 minutes
 - ◆ Can be done at any time of the day
 - ◆ Can use IM if IV is not possible
 - ◆ Normal: peak serum cortisol ≥ 18 mcg (497 nmol)

Diagnosis of adrenal insufficiency

- If patient is acutely sick:
 - ◆ Start treatment; do not wait for results
 - ◆ If test will delay treatment, start treatment then do the test later when the patient is stable
- Plasma aldosterone & renin: (in primary disease)
 - ◆ Low aldosterone and high renin in primary disease

Treatment of adrenal insufficiency

- All patients (1^{ry} & 2^{ry}) require glucocorticoids:
 - **Hydrocortisone** (15-25 mg/d) divided in 2-3 doses/day (depends on patient's weight)
10 am, 5 pm or 15 am, 5 pm or 15 am, 10 pm
- Some will feel fatigue at night or morning: give 3 doses
 - 10 mg am, 5 mg afternoon, 5 mg evening
 - or 15 mg am, 5 mg afternoon, 5 mg pm
- Slow-release form (once daily at am) is available

Alternative treatment of adrenal insufficiency

- **Prednisone** or **Prednisolone** (2.5-7.5 mg/d) 1-2 times/day
 - Use if patient is not compliant with multiple daily doses
 - or in those with late-evening or early morning symptoms that are not relieved by three-times daily hydrocortisone

Monitoring of treatment for adrenal insufficiency

- Symptoms (energy level, headache, dizziness)
- Watch also for symptoms/signs of high dose (increased weight, puffy face)
- Clinical (weight, postural BP, edema)
- Hormonal monitoring is **not** recommended

Mineralocorticoids treatment in **primary** adrenal insufficiency

- Patients with aldosterone deficiency:
 - Should received mineralocorticoid replacement
 - Fludrocortisone (50-100 micrograms/day)
- Monitoring:
 - Clinical assessment (salt craving, postural hypotension, edema)
 - Blood electrolytes

Glucocorticoids potency

- 20 mg Hydrocortisone =
- 5 mg Prednisone/Prednisolone =
- 4 mg Methylprednisolone =
- 0.75 mg Dexamethasone

Cushing's syndrome

Clinical features of Cushing's Syndrome

- Weight gain
- Skin infections
- Fatigue
- Mood changes
- Depression
- Decreased libido
- Hirsutism

Physical findings in Cushing's Syndrome

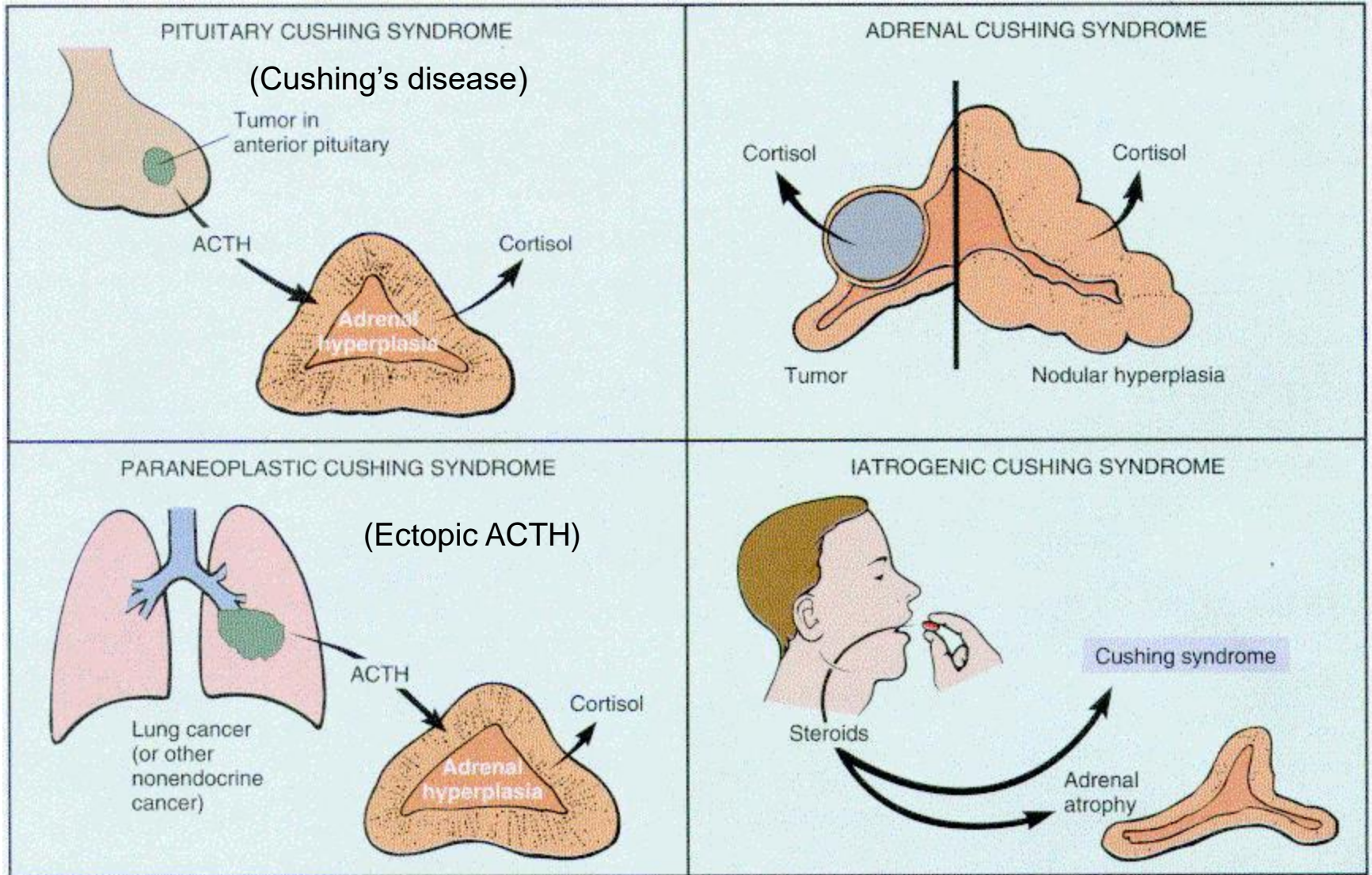
- Facial plethora
- Moon facies
- Supra-calvicular fat pads
- Central obesity
- Proximal muscle weakness
- Wide (> 1 cm), purple or red striae
- Spontaneous ecchymoses



Associations with Cushing's Syndrome

- Hypertension
- Diabetes mellitus
- Osteoporosis
- Hypogonadism
- Poor wound healing
- Kidney stones

Causes of Cushing's syndrome



When to suspect Cushing's syndrome?

- Clinical features of Cushing's syndrome , especially facial plethora, proximal myopathy, striae (>1 cm wide and red or purple), easy bruising
- Unusual findings such as osteoporosis or hypertension in young adults
- Unexplained severe features (resistant hypertension, osteoporosis) at any age
- Adrenal incidentaloma
- **Always take a full history on the use of steroids (oral, inhalers, local, injections)**

Diagnosis of Cushing's syndrome

- The following tests have been used (1 or more):

1) 24-hour urinary free cortisol

- Is usually > 3-fold the upper limit of normal to suspect Cushing's syndrome

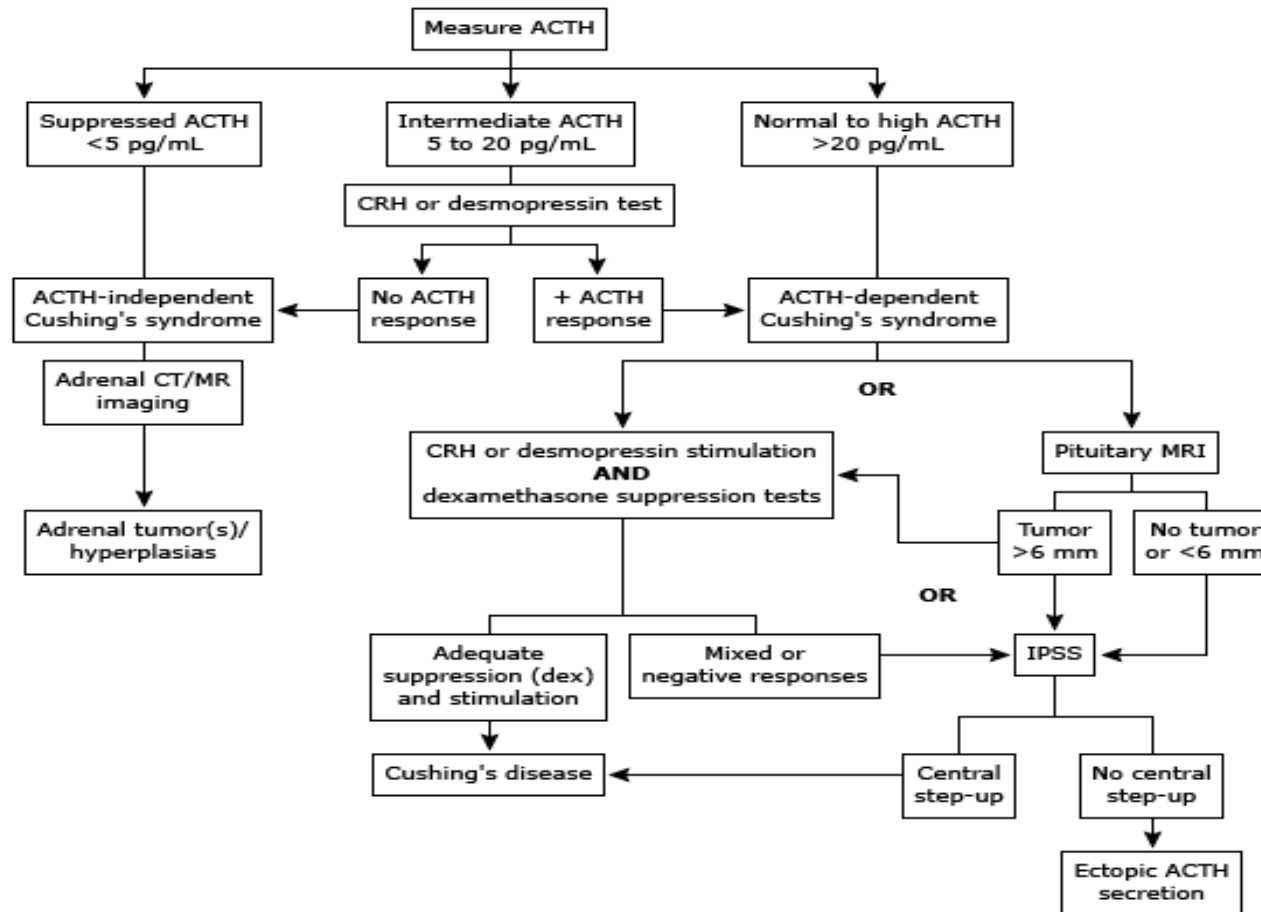
2) Late-night salivary cortisol

- Different cutoffs depending on the used assay

3) Overnight 1 mg dexamethasone suppression test:

- 1 mg of dexamethasone orally at 11 PM to 12 AM
- Check serum cortisol next day at 8 AM [Normal < 50 nmol (1.8 mcg)]

Establishing the cause of Cushing's syndrome



Primary aldosteronism

Features of primary hyperaldosteronism

- Hypertension
 - A common cause of secondary HTN
- Hypokalemia
 - Not in all patients
- Metabolic alkalosis
- Mild hypernatremia
- Hypomagnesemia
- Muscle weakness
- Higher rate of cardiovascular morbidity & mortality

Causes of primary hyperaldosteronism

- **Bilateral idiopathic hyperaldosteronism** (or idiopathic hyperplasia [IHA] (60-70%))
- **Unilateral aldosterone-producing adenoma [APA]** (30-40%)
- Unilateral hyperplasia or primary adrenal hyperplasia
- Familial hyperaldosteronism type I
(glucocorticoid-remediable aldosteronism) [GRA]
- Aldosterone-producing adrenocortical carcinomas, ectopic aldosterone-secreting tumors

When to test for primary hyperaldosteronism?

- Resistant hypertension
- When secondary hypertension is suspected
- Hypertension with adrenal incidentaloma
- Hypertension with sleep apnea
- Hypertension and a family history of early-onset hypertension
- All hypertensive first-degree relatives of patients with primary aldosteronism

Diagnosis of primary hyperaldosteronism

1) Screening test:

- Plasma aldosterone concentration (PAC):
 - High or normal
 - ≥ 10 ng/dL (277 pmol/L)
- Plasma renin activity (PRA) or concentration (PRC):
 - Low
 - [PRA < 1 ng/mL/hour] or [PRC $<$ lower limit of normal]
- Ratio (PAC/PRA) or (PAC/PRC):
 - High
 - > 20

Diagnosis of primary hyperaldosteronism (2)

2) Confirmatory test:

- Oral sodium loading or saline infusion test

A) Oral sodium loading:

- Sodium normally suppresses aldosterone
- Aldosterone does not suppress in 1^{ry} aldosteronism
- 2 grams sodium chloride tablets three times daily × 3 days
- 24-hour urine sodium [should be >200 mEq (4600 mg) to document adequate sodium loading]
- 24-hour urine aldosterone >12 mcg (33 nmol) confirms primary hyperaldosteronism

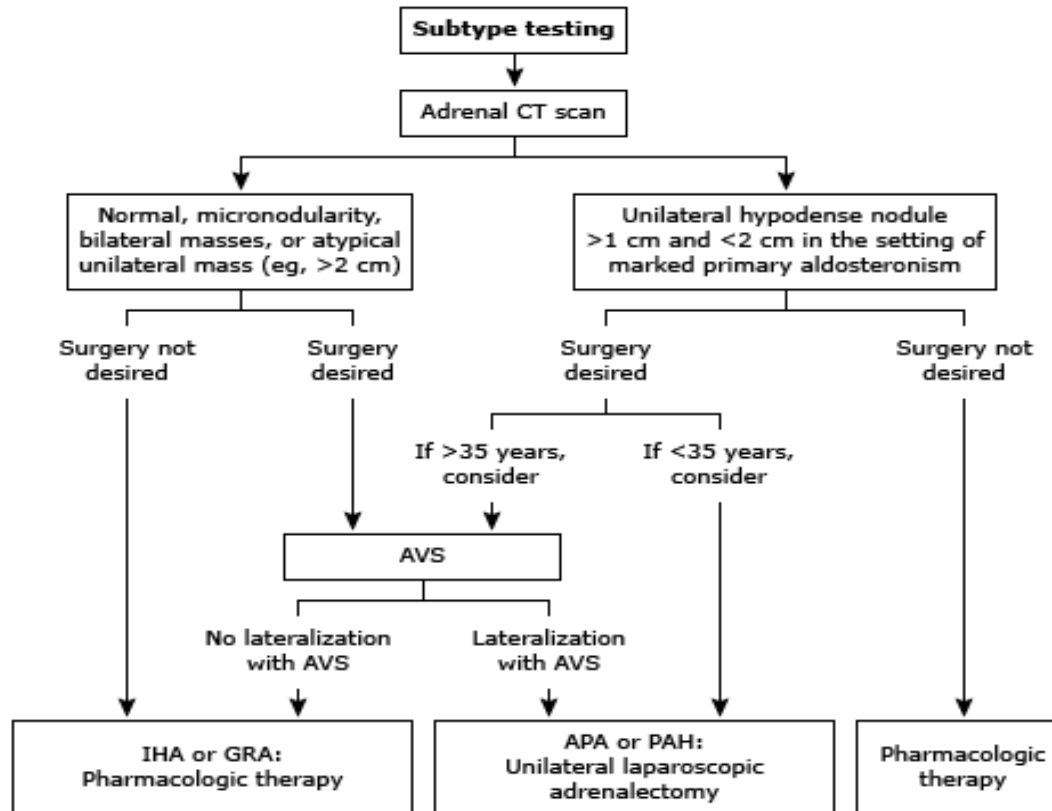
Diagnosis of primary hyperaldosteronism (3)

2) Confirmatory test:

B) Saline infusion test :

- Sodium normally suppresses aldosterone
- IV infusion of 2 Liters of isotonic saline over 4 hours (from 8 AM to 12 PM), ideally while the patient is seated
- Plasma aldosterone at end of infusion: > 10 ng/dL (277 pmol/L) confirms primary aldosteronism

Determining the subtype of primary aldosteronism



AVS: adrenal venous sampling; IHA: idiopathic hyperaldosteronism; GRA: glucocorticoid-remediable aldosteronism; APA: aldosterone-producing adenoma; PAH: primary adrenal hyperplasia

pheochromocytoma

Pheochromocytoma

- Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla
- Catecholamine-secreting paragangliomas are tumors that arise from the sympathetic ganglia. Also called "extra-adrenal pheochromocytomas"
- Occurs in 0.2% of cases of hypertension

Associations with pheochromocytoma

- There are several familial disorders that are associated with pheochromocytoma
- All have autosomal dominant inheritance
- **Multiple endocrine neoplasia type 2 (MEN2A & MEN2B)**
- **von Hippel-Lindau (VHL) syndrome**
- **Neurofibromatosis type 1 (NF1)**

Symptoms of pheochromocytoma

- **Triad of: headache, sweating, palpitations**
 - Most patients do not have all the 3 symptoms
 - Headache (up to 90% of symptomatic patients)
 - Sweating (up to 60-70% of symptomatic patients)
- **Other symptoms** may include:
 - Palpitations, tremor, pallor, dyspnea, generalized weakness, panic attack, blurred vision, weight loss, polyuria, polydipsia, constipation
- **Asymptomatic:**
 - During evaluation of an adrenal incidentaloma or on screening for familial disorder or family history

Clinical features of pheochromocytoma

- **Sustained or paroxysmal hypertension:**
 - The commonest sign
 - But 5 to 15% of patients have normal BP
- **Paroxysmal elevations in BP** during diagnostic procedures, surgery, or with drugs (such as beta blockers, tricyclic antidepressants, corticosteroids)
- Orthostatic hypotension, papilledema
- Insulin resistance, hyperglycemia, leukocytosis

When to suspect pheochromocytoma?

- Headache, sweating & palpitations (with or without HTN)
- Hyperadrenergic spells (palpitations, diaphoresis, headache, tremor, or pallor)
- When secondary hypertension is suspected
- Resistant hypertension
- A familial syndrome (multiple endocrine neoplasia type 2, neurofibromatosis type 1 or von Hippel-Lindau)
- A family history of pheochromocytoma
- Adrenal incidentaloma with or without hypertension
- ↑↑ BP response during anesthesia, surgery, or procedure

Interfering medications with testing for pheochromocytoma

- Falsely elevated urinary and/or plasma metanephrines:
 - Acetaminophen
 - Labetalol
 - Sotalol
 - Methyldopa
 - Tricyclic antidepressants
 - Buspirone
 - Phenoxybenzamine
 - MAO-inhibitors, sympathomimetics, cocaine
 - Sulphasalazine
 - Levodopa

Diagnosis of pheochromocytomas

- 24-hour urinary fractionated catecholamines (dopamine, norepinephrine and epinephrine), fractionated metanephrines (metanephrine , normetanephrine) and creatinine
- This is the usual test done in most centers
- Creatinine is done to assure adequate sample
- Values are usually are $> 2-3$ times upper limit of normal

Diagnosis of pheochromocytomas (2)

- **Plasma fractionated metanephrines**
 - Is helpful when it is normal (high sensitivity)
 - But it has a high false positive rate (lower specificity)
 - Suggested if there's high suspicion for pheochromocytoma:
 - A family history of pheochromocytoma
 - A genetic syndrome (such as MEN2)
 - A past history of resected pheochromocytoma
 - An incidentally discovered adrenal mass that has imaging characteristics consistent with pheochromocytoma

Diagnosis of pheochromocytomas: Plasma fractionated metanephrines

- Overnight fast
- Place IV cannula
- Patient stays **supine** for 20 minutes
- Then draw blood
- The cutoffs to exclude pheochromocytoma:
 - Metanephrine <0.3 nmol/L and/or
normetanephrine <0.66 nmol/L

What if results are indeterminate?

- For patients with mildly high results
- Repeat testing during symptoms (if they exist)
- Obtain (or repeat) plasma fractionated metanephrines
- Or repeat 24-hour urinary fractionated catecholamines, metanephrines and creatinine
- Re-assess after 6 months

Localization of pheochromocytomas

- This is done only after biochemical confirmation of pheochromocytoma is achieved
- **CT-scan** (preferred)
- **MRI** for:
 - Metastatic pheochromocytoma
 - For detection of skull base and neck paragangliomas
 - Patients with surgical clips that cause artifacts when using CT
 - Patients with an allergy to CT contrast
 - Patients in whom radiation exposure should be limited (children, pregnancy)
 - Patients with known germline mutations
 - Patients with recent excessive radiation exposure

Localization of pheochromocytomas

- **If imaging is negative, consider:**
 - Re-assess the diagnosis
 - Whole body MRI
 - or
 - FDG-PET scan
 - or
 - Iobenguane I¹²³ scan [also called metaiodobenzylguanidine (MIBG)]

Treatment of pheochromocytomas

- Surgical resection
- Preoperative management:
 - 1) Alpha-adrenergic blockade:**
 - Phenoxybenzamine, prazosin, terazosin or doxazosin
 - Start 1-2 weeks before surgery
 - Adjust per BP
 - 2) Beta-adrenergic blockade:**
 - Start 2-3 days before surgery
 - Never start alone (can lead to unopposed alpha-adrenergic stimulation causing increase in BP)
 - Propranolol or metoprolol (adjust per pulse, BP)

Treatment of pheochromocytomas (2)

- Preoperative management:

- 3) **High-sodium diet and fluid intake:**

- To reverse catecholamine-induced blood volume contraction preoperatively
 - To prevent severe hypotension after tumor removal

- Post-operative management:

- Monitor blood pressure, heart rate, and blood glucose

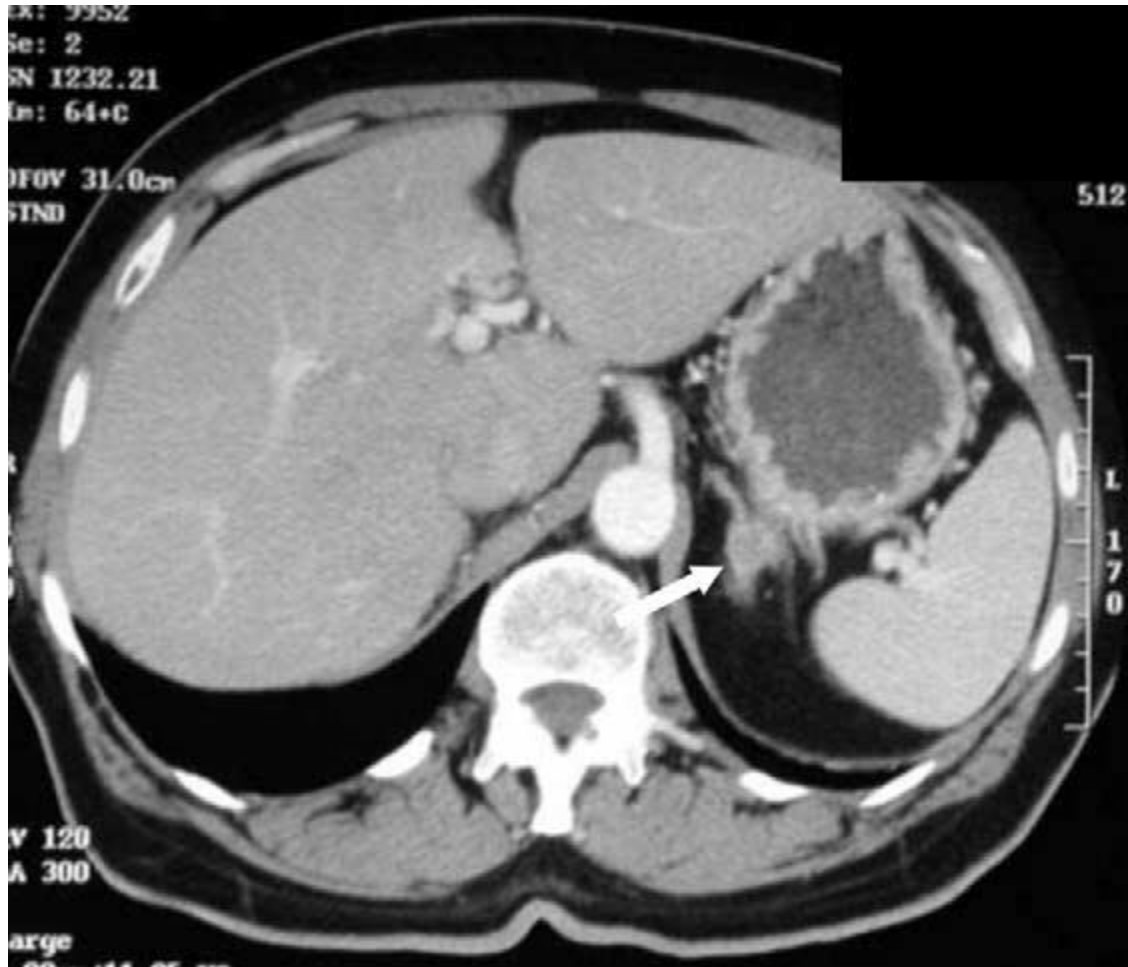
- Follow up:

- Lifelong annual biochemical testing to assess for recurrent or metastatic disease

Adrenal incidentaloma

Incidentally-discovered adrenal mass (Adrenal incidentaloma)

- > 1 cm in size, discovered incidentally on imaging
- Prevalence 4.4%. In the elderly: 10%
- Rule out pheochromocytoma (urine or plasma catecholamines, metanephrines)
- Rule out Cushing's syndrome (usually subclinical; 1-mg dexamethasone suppression test is more sensitive)
- If HTN, rule out primary aldosteronism (serum aldosterone, plasma renin activity)



**Left adrenal mass found
incidentally on CT-scan**

Adrenal mass

Functional

Surgery

Non-functional

Suspicious features
on imaging

- Consider surgery
- FNA# if suspecting metastasis or infection

Benign features
on imaging

- Repeat imaging at 1 year
- Yearly DST* × 4 years

Progression

- Growth by ≥ 1 cm
- Size grows to ≥ 4 cm
- Abnormal DST*

Consider surgery

* DST = dexamethasone suppression test

Rule out pheo before doing FNA