Adrenal disorders

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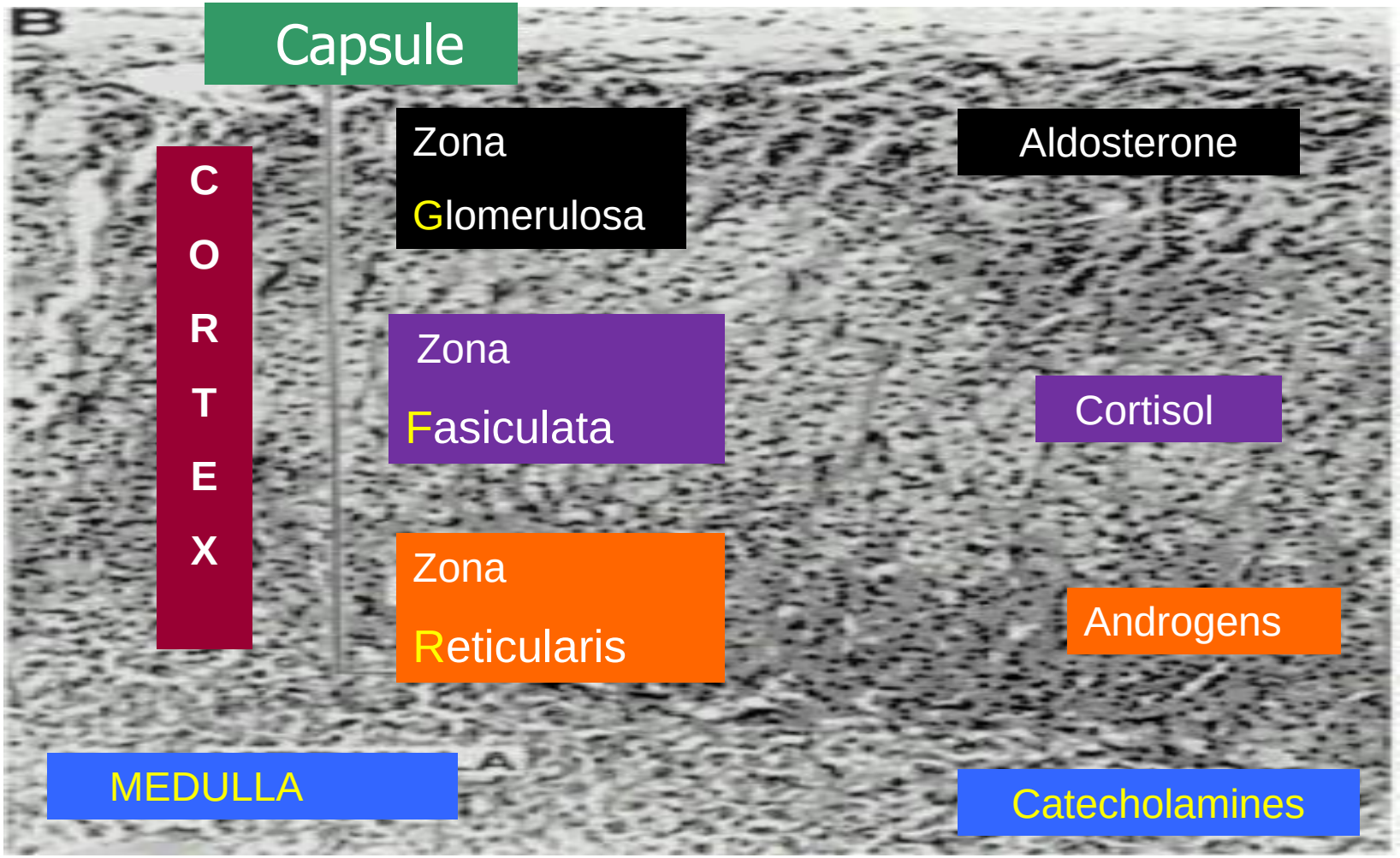
Histology of the Adrenal gland



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
- The diagnosis of adrenal insufficiency is usually delayed

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:**
  - Weakness
  - Abdominal pain
  - Fever
  - Hypotension
  - Confusion
  - Coma

Laboratory findings in adrenal insufficiency

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

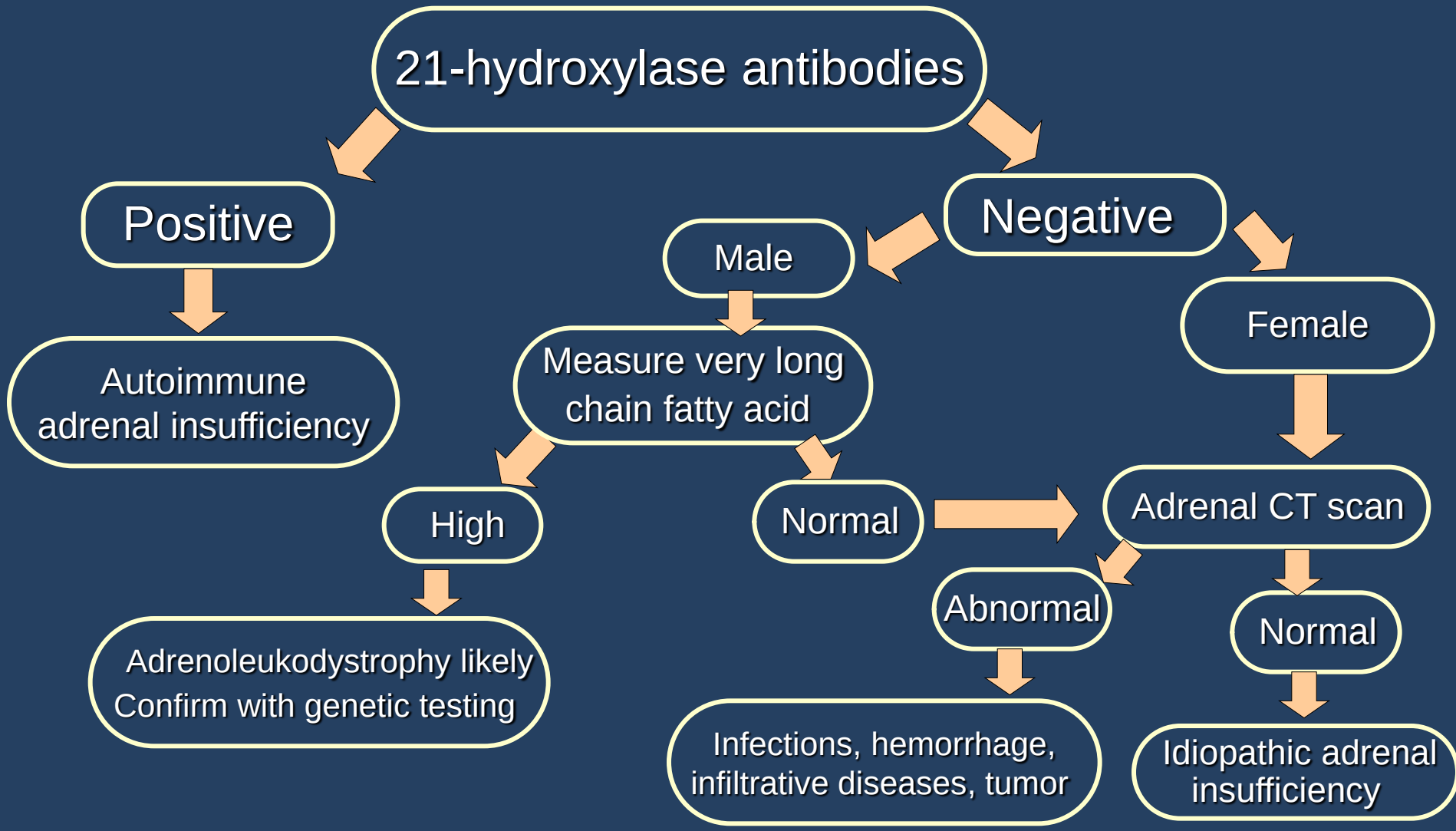
Causes of adrenal insufficiency

- **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
- Infections (such as TB, fungi, HIV)
- Hemorrhage
- Infiltrative diseases
- Malignancy, metastasis
- Medications (ketoconazole, mitotane, metyrapone)

Investigating the cause of primary adrenal insufficiency



Causes of secondary adrenal insufficiency

- Hypopituitarism caused by pituitary tumors, infections (TB, fungi), infiltrative diseases, hemorrhage, lymphocytic hypophysitis
- Autoimmune
- Traumatic brain injury
- Isolated ACTH deficiency

Causes of tertiary adrenal insufficiency

1) Abrupt cessation of high-dose glucocorticoids:
   - They decrease CRH
2) 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
3) Tumors, infiltrative diseases (sarcoidosis), cranial radiation

Diagnosis of adrenal insufficiency

- Serum cortisol (8-9 am) < 3 mcg (83 nmol) highly suggests adrenal insufficiency
- Plasma ACTH level (if available):
  - High (> 2-fold upper limit) = primary insufficiency
  - Normal or low = secondary insufficiency
- AM cortisol ≥ 18 mcg (500 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 min. after injection
  - Can be done at any time of the day
  - If doing ACTH, do the test in early morning
  - Can use IM if IV is not possible
  - Normal: peak serum cortisol ≥18 μg (500 nmol)

Diagnosis of adrenal insufficiency

- **Plasma aldosterone & renin:**

  - Low aldosterone and high renin in primary disease

  - Normal levels in secondary disease

- **DHEAS:**

  - Low in primary & secondary disease; confirms the diagnosis

  - Use if ACTH stimulation test result is indeterminate

Treatment of suspected adrenal insufficiency

- **If the patient is acutely ill:**
  - If possible, draw serum cortisol before treatment
  - Start treatment; do not wait for results
  - If test will delay treatment, start treatment then do testing later when the patient is stable
  - Hydrocortisone 100 mg IV then 50 mg every 6 hours
  - If hydrocortisone is not available, use prednisolone

Treatment of chronic 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)
- Twice daily: 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 am, 5 afternoon, 5 evening
  - or 15/5/5
- Slow-release form (once daily at am) is available
- Alternatively, can use cortisone acetate (20-35 mg/day)

Endocrine Society guidelines. J Clin Endocrinol Metab 2016;116:301

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 glucocorticoids 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 (↓aldosterone, ↑renin):
  - Should received mineralocorticoid replacement
  - Fludrocortisone (50-100 micrograms/day)
- Monitoring:
  - Clinical assessment (salt craving, postural hypotension, edema)
  - Serum electrolytes

DHEA treatment in primary adrenal insufficiency

- DHEA = dehydroepiandrosterone
- DHEA is recommended in women with primary adrenal insufficiency with low libido, depressive symptoms, or low energy levels despite optimized glucocorticoid & mineralocorticoids
- DHEA 25-50 mg daily
- Monitoring by measuring morning serum DHEAS aiming at mid-normal range before taking DHEA tablet
- If no improvement after 6 months, stop treatment

Endocrine Society guidelines. J Clin Endocrinol Metab 2016;116:301

Glucocorticoids potency

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

Cushing’s syndrome

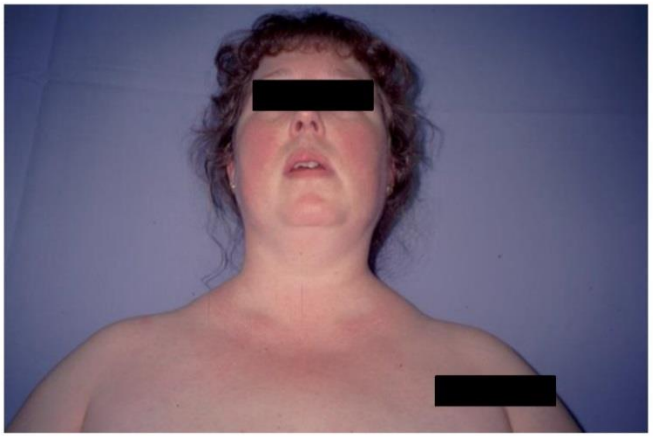
Clinical features of Cushing's Syndrome

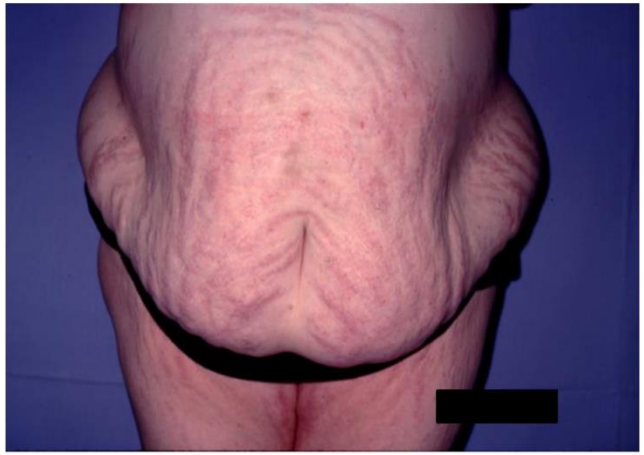
- Weight gain
- Skin infections
- Fatigue
- Mood changes
- Depression
- Decreased libido
- Hirsutism

Nieman LK. Eur J Endocrinol 2015;173:M33

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

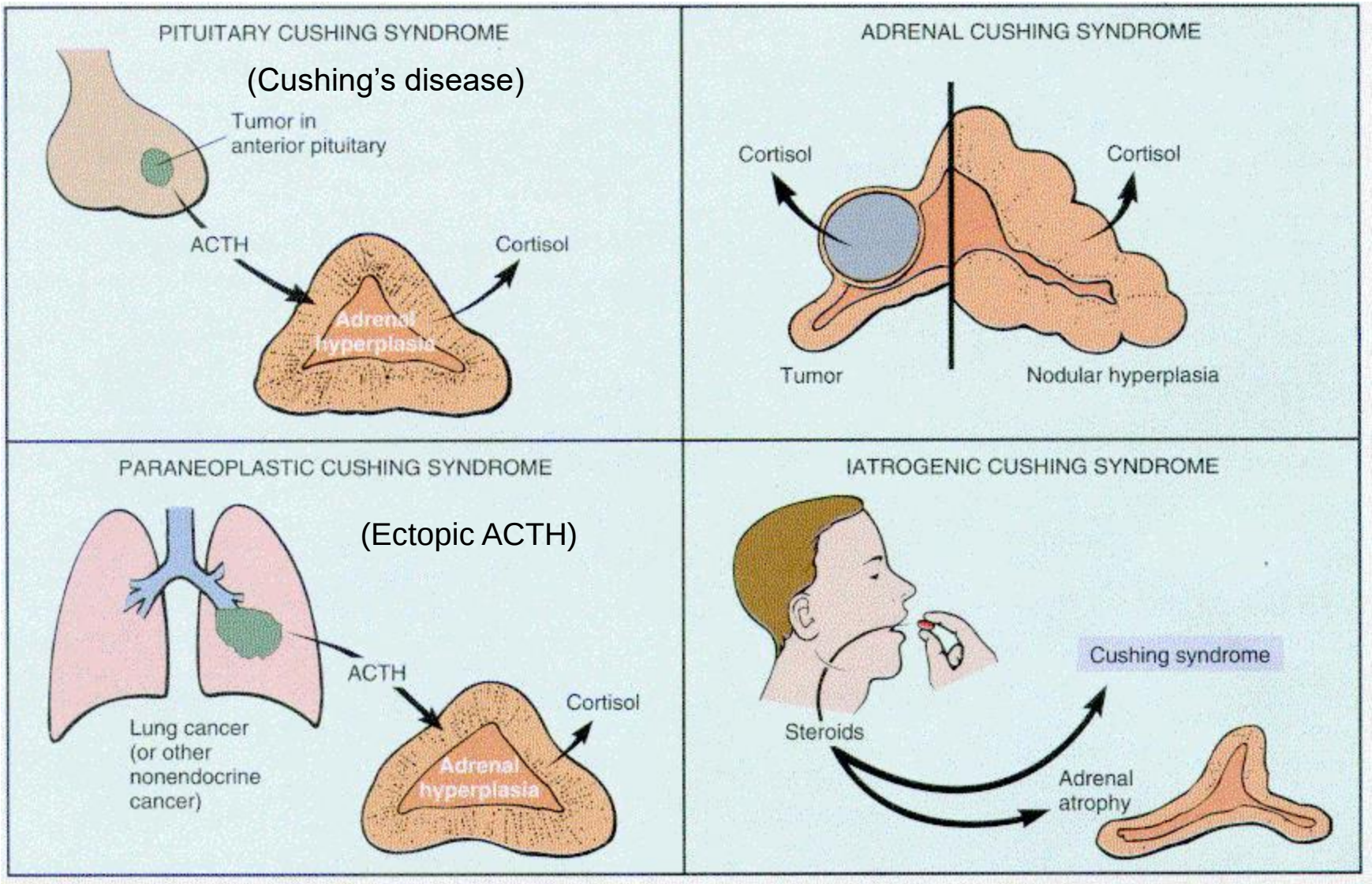




Associations with Cushing's Syndrome

- 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):

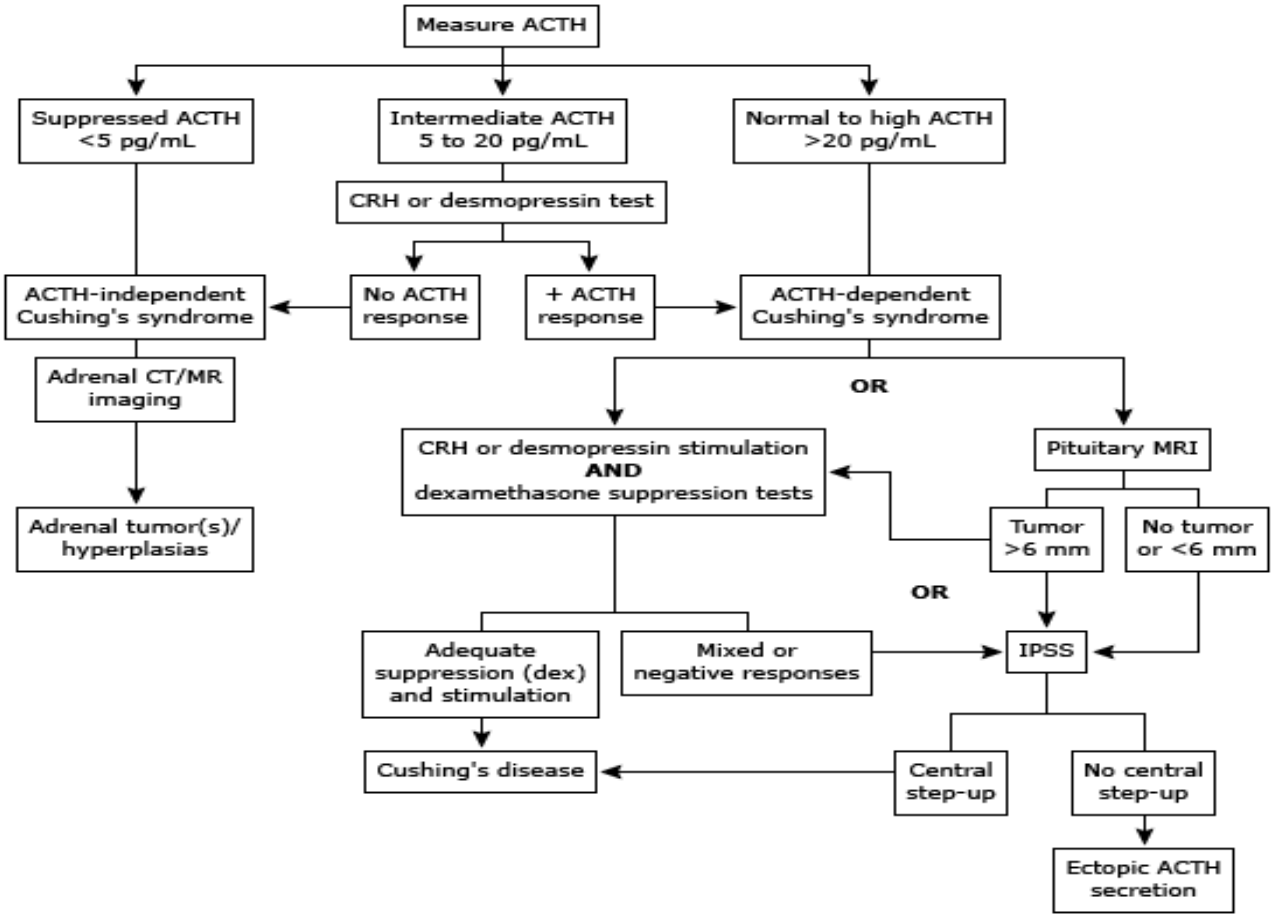
1) 24-hour urinary free cortisol
   - Is usually >3-fold the upper limit of normal to suspect Cushing's syndrome

2) 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)]

3) Late-night salivary cortisol
   - Different cutoffs depending on the used assay

Endocrine Society guidelines. J Clin Endocrinol Metab 2008;93:1526

Establishing the cause of Cushing's syndrome



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IPSS: inferior petrosal sinus sampling

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

Endocrine Society guideline. J Clin Endocrinol Metab 2016;101:1889

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

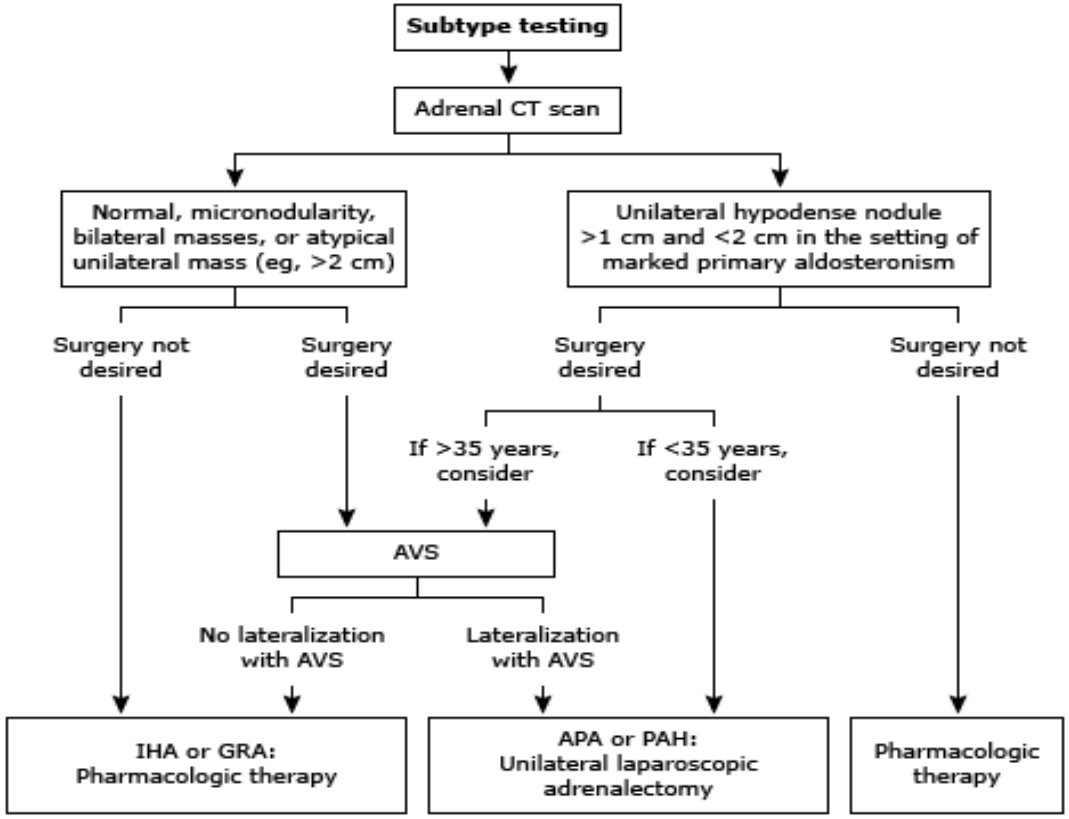
Diagnosis of primary hyperaldosteronism (3)

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



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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 > 2-3 times upper limit of normal

Endocrine Society guideline. J Clin Endocrinol Metab 2014; 99: 1915

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 I^{123} 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

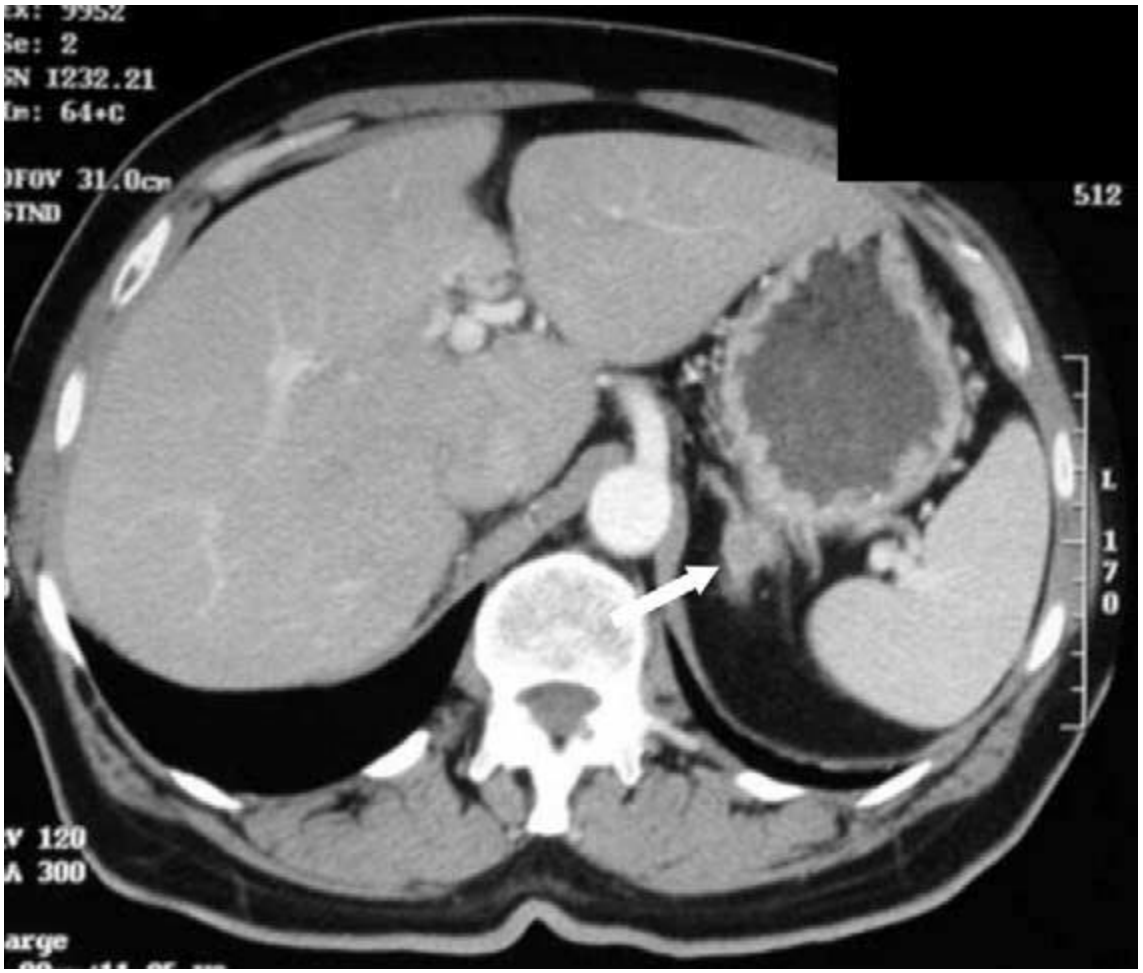
- **Follow up:**

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

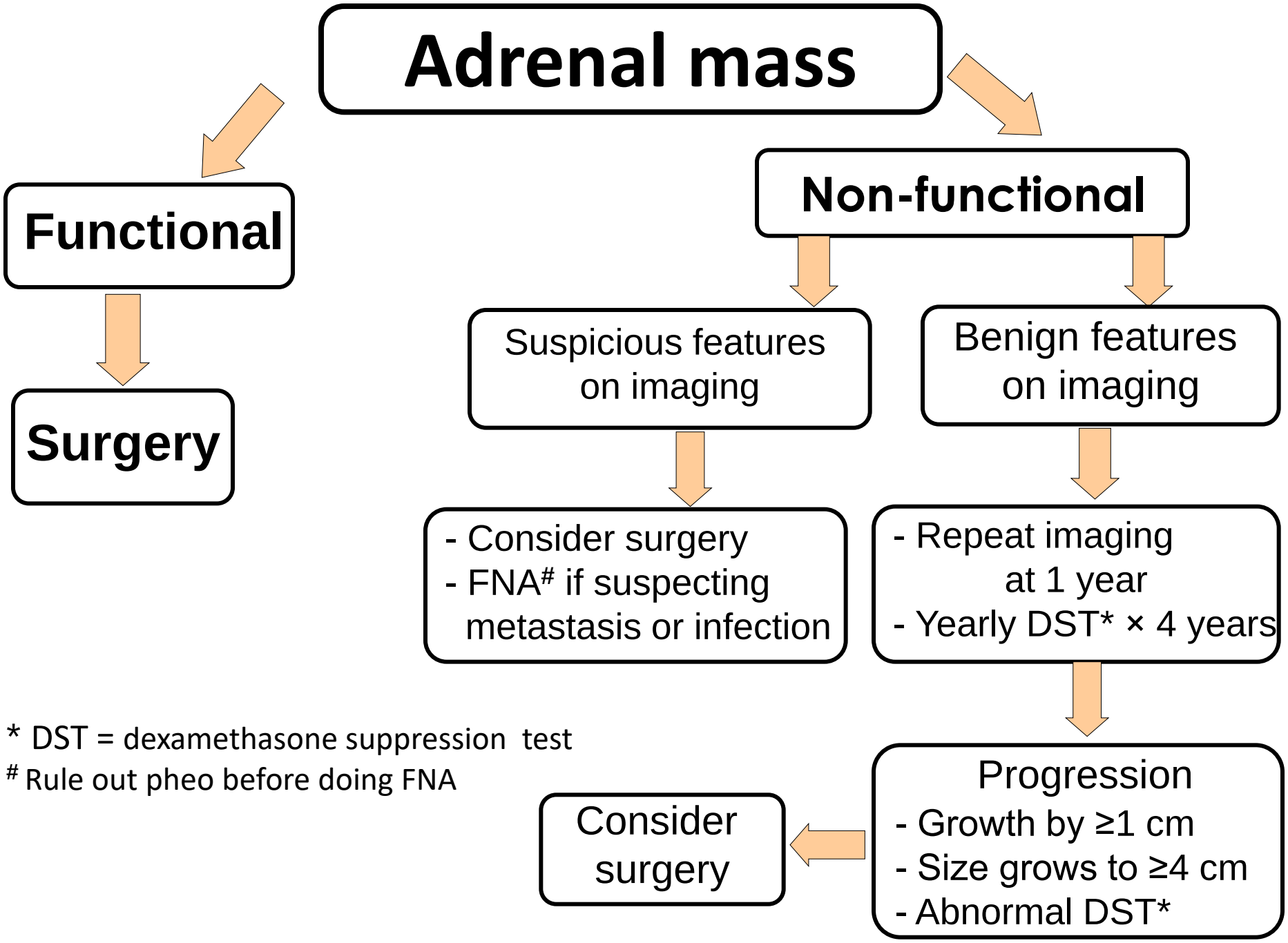
Adrenal incidentaloma

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



* DST = dexamethasone suppression test

Rule out pheo before doing FNA

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