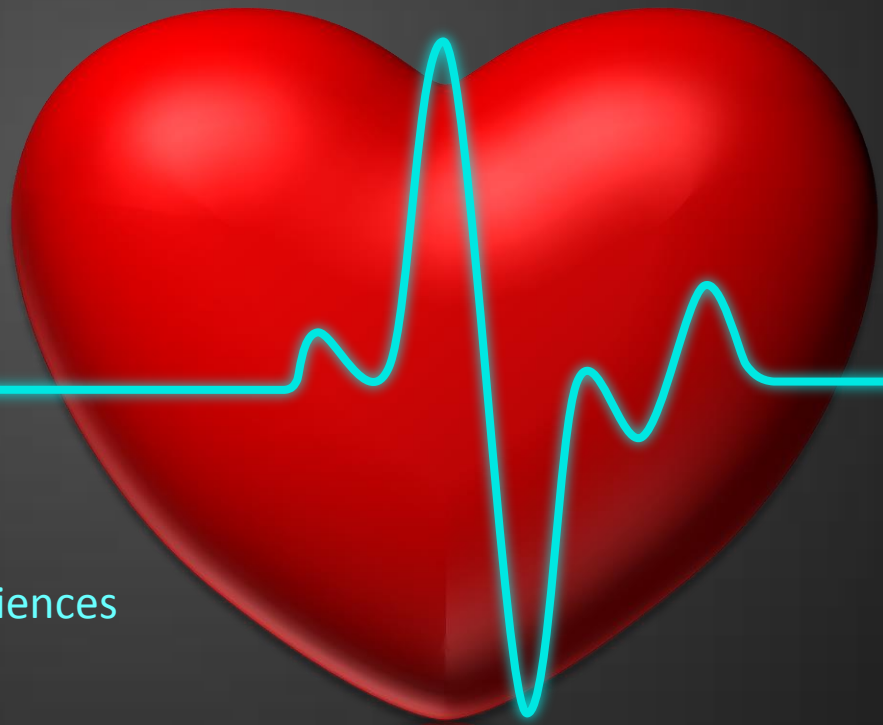
# Endocrine Causes of Hypertension in Children

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## TABLE 16.1 Endocrine Causes of Hypertension

### Adrenal-Dependent Causes

Pheochromocytoma
Primary aldosteronism
Hyperdeoxycorticosteronism
- Congenital adrenal hyperplasia
- 11β-Hydroxylase deficiency
- 17α-Hydroxylase deficiency
- Deoxycorticosterone-producing tumor

Primary cortisol resistance
Cushing syndrome

### AME/11βHSD Deficiency

Genetic
- Type 1 AME
- Type 2 AME

Acquired
- Licorice or carbenoxolone ingestion (type 1 AME)
- Cushing syndrome (type 2 AME)

### Thyroid-Dependent Causes

Hypothyroidism
Hyperthyroidism

### Renin-Secreting Tumor

### Pituitary-Dependent Causes

Acromegaly
Cushing syndrome

# Case 1

A 10 y/o boy is PICU admission due to LOC and BP 18o/120
history of common cold with and headache and abdominal pain
Drug history acetaminophen and pseudoephedrine
familial history of medullary thyroid carcinoma surgery in his father.

1)What is your diagnosis?
2)What is your lab data and imaging study comments?
3)Which anti hypertensive drugs are choice?

# Pheochromocytoma

The most common site of origin (approximately 90%) is the adrenal medulla (more often on the right side).

In more than 20% of affected children; bilateral adrenal tumors most in 30–40% of children, tumors are found in both adrenal and extra adrenal areas or only in an extra adrenal area.

frequently between 6 and 14 yr of age.

associated with genetic syndromes such as Von Hippel-Lindau disease, Multiple endocrine neoplasia 2A,2B, Neurofibromatosis (type 1), Tuberous sclerosis, Ataxia telangiectasia, Sturge weber, congenital polycitemia, cyanotic congenital heart disease

## TABLE 16.2 Signs and Symptoms Associated With Catecholamine-Secreting Tumors

### Spell-Related Signs and Symptoms

Anxiety and fear of impending death
Diaphoresis
Dyspnea
Epigastric and chest pain
Headache
Hypertension
Nausea and vomiting
Pallor
Palpitation (forceful heartbeat)
Tremor

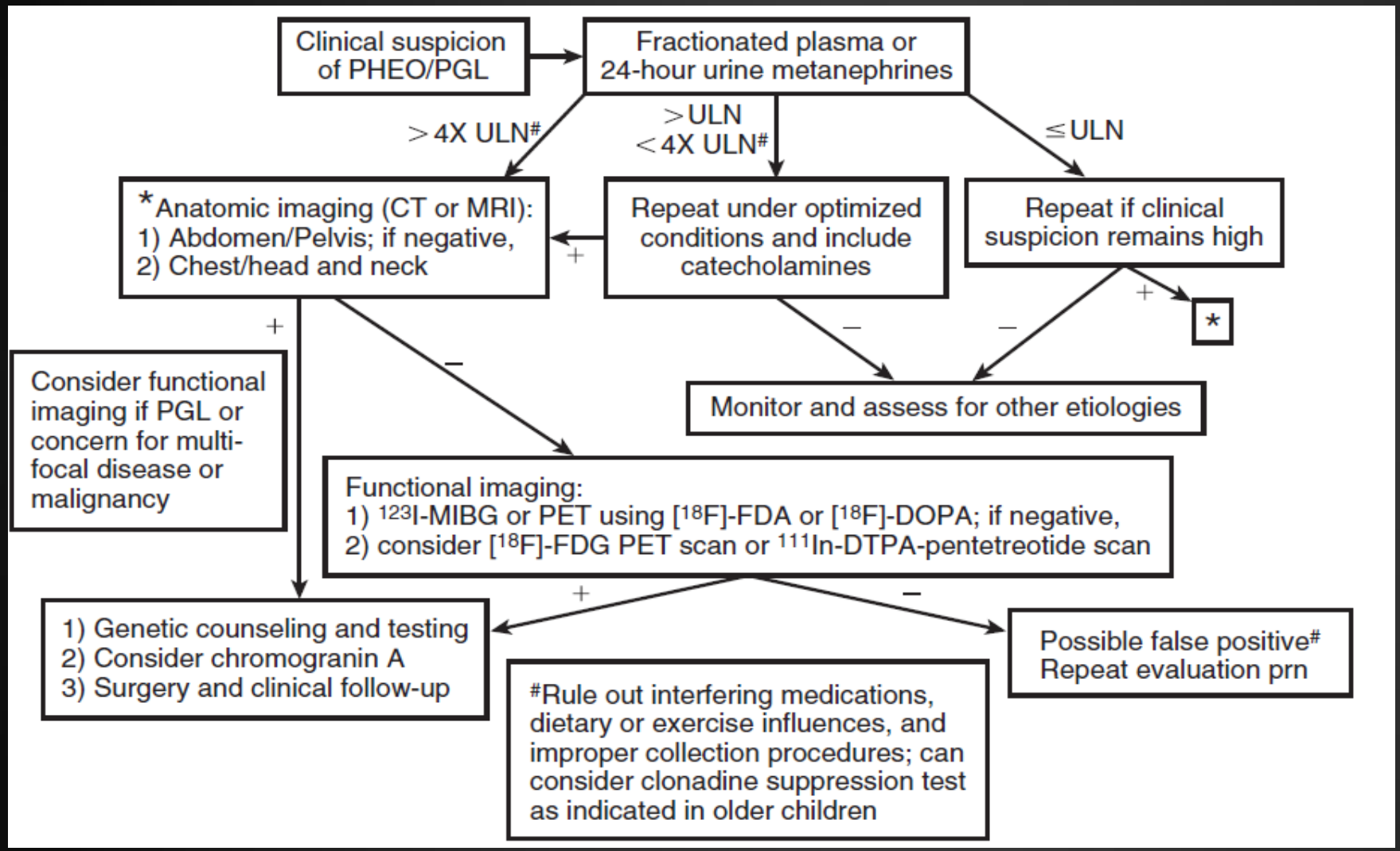
### Chronic Signs and Symptoms

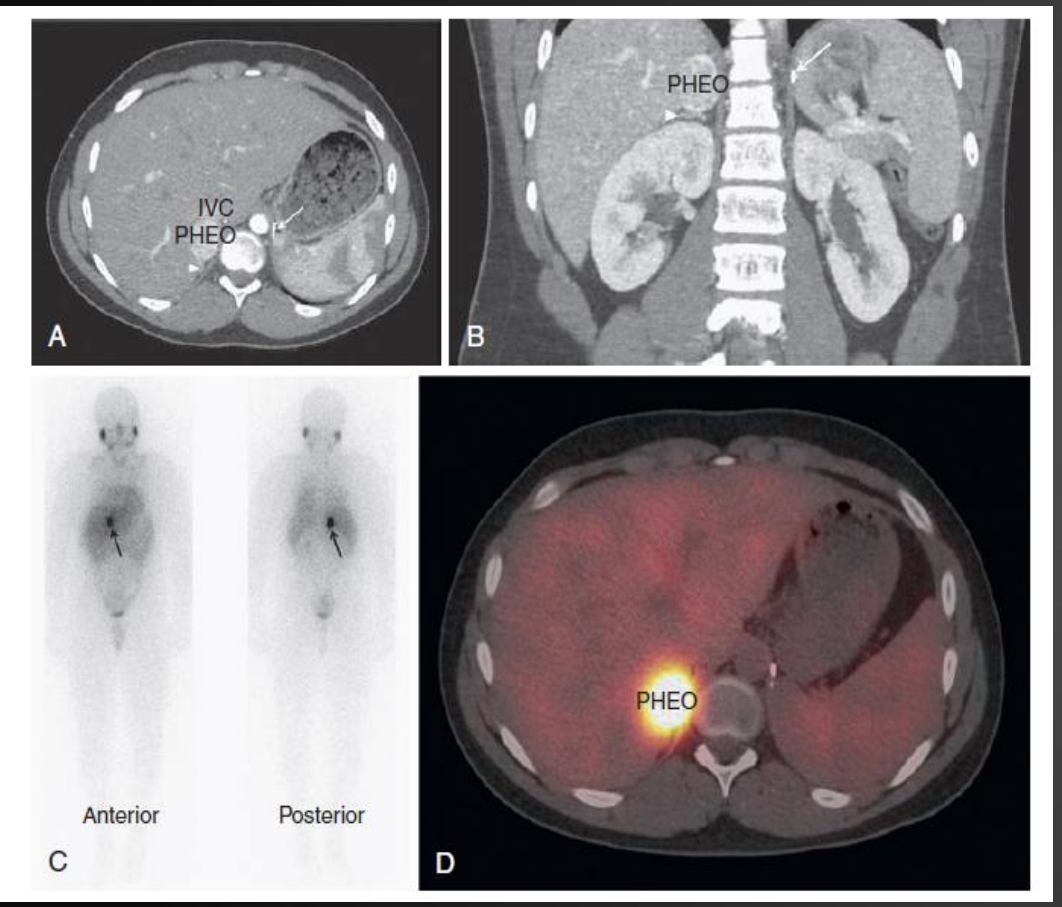
Cold hands and feet
Congestive heart failure—dilated or hypertrophic cardiomyopathy
Constipation
Diaphoresis
Dyspnea
Ectopic hormone secretion–dependent symptoms (e.g., CRH/ACTH, GHRH, PTHrP, VIP)
Epigastric and chest pain
Fatigue
Fever
General increase in sweating
Grade II to IV hypertensive retinopathy
Headache
Hyperglycemia
Hypertension
Nausea and vomiting
Orthostatic hypotension
Painless hematuria (associated with urinary bladder paraganglioma)
Pallor
Palpitation (forceful heartbeat)
Tremor
Weight loss

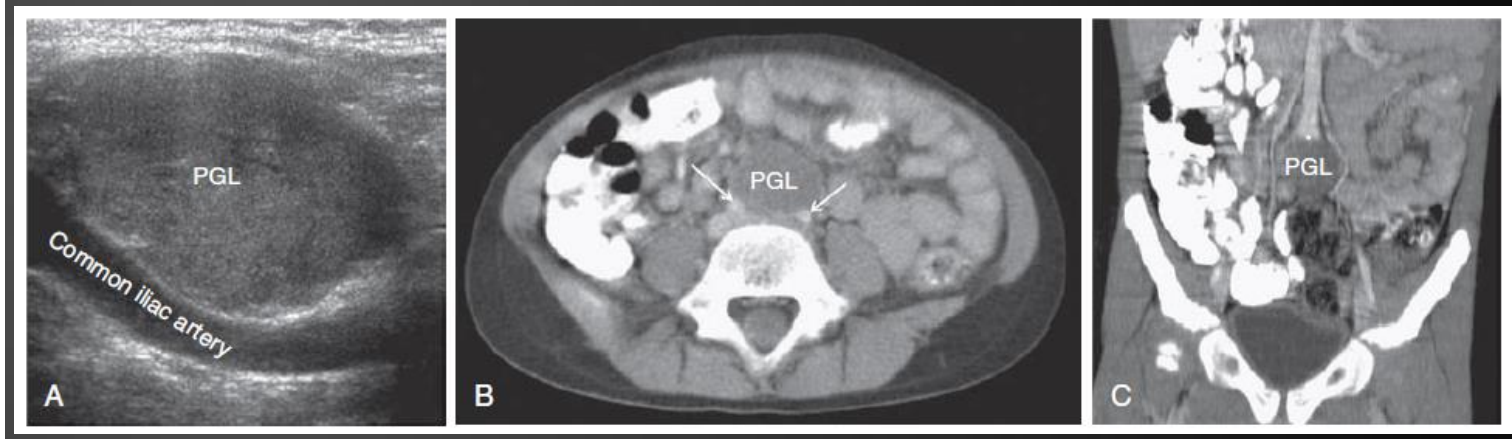
### Not Typical of Pheochromocytoma

Flushing

# Diagnosis of pediatric pheochromocytoma/paraganglioma




IVC
PHEO
A
PHEO
B
Anterior
Posterior
C
PHEO
D


PGL
Common iliac artery
A
PGL
B
PGL
C

## TABLE 14-3 Preoperative Medical Management of Pheochromocytoma/Sympathetic Paraganglioma

| Drug Class | Drug | Mechanism of Action | Initial Pediatric Dose |
|---|---|---|---|
| α-adrenergic receptor blockers | Doxazosin | $\alpha_1$-antagonist | 0.5-1 mg daily |
| | Phenoxybenzamine | $\alpha_1$- and $\alpha_2$-antagonist | 0.2-0.5 mg/kg/day divided BID (max 10 mg BID) |
| | Prazosin | $\alpha_1$-antagonist | 0.05-0.1 mg/kg/day divided TID (max 1 mg TID) |
| β-adrenergic receptor blockers | Atenolol | $\beta_1$- antagonist | 0.5-1 mg/kg/dose daily (max 50 mg daily) |
| | Metoprolol | $\beta_1$- antagonist | 1-2 mg/kg/day divided BID (max 50 mg BID) |
| | Propranolol | $\beta_1$- and $\beta_2$-antagonist | 0.5-1 mg/kg/day divided BID (max 40 mg BID) |
| Calcium channel blockers | Nifedipine (sustained release) | Calcium channel blocker | 0.25-0.5 mg/kg/day daily or BID (max 60 mg total daily dose) |
| Inhibitors of catecholamine synthesis | Metyrosine | Tyrosine hydroxylase inhibitor | 125-250 mg divided BID-TID |

## TABLE 16.9 Intravenously Administered Drugs Used to Treat Pheochromocytoma

| Agent | Dosage Range |
|---|---|
| **For Hypertension** | |
| Phentolamine | Administer a 1-mg IV test dose, then 2-mg to 5-mg IV boluses as needed or continuous infusion. |
| Nitroprusside | IV infusion rates of 2 μg/kg of body weight per minute are suggested as safe. Rates >4 μg/kg per minute may lead to cyanide toxicity within 3 hours. Doses >10 μg/kg per minute are rarely required, and the maximal dose should not exceed 800 μg/min. |
| Nicardipine | Initiate therapy at 5 mg/hr; the IV infusion rate may be increased by 2.5 mg/hr q15 min up to a maximum of 15 mg/hr. |
| **For Cardiac Arrhythmia** | |
| Lidocaine | Initiate therapy with an IV bolus of 1—1.5 mg/kg (75—100 mg); additional boluses of 0.5—0.75 mg/kg (25—50 mg) can be given q5—10 min if needed up to a maximum of 3 mg/kg. Loading is followed by maintenance IV infusion of 2—4 mg/min (30—50 μg/kg per minute) adjusted for effect and settings of altered metabolism (e.g., heart failure, liver congestion) and as guided by blood level monitoring. |
| Esmolol | An initial IV loading dose of 0.5 mg/kg is infused over 1 minute, followed by a maintenance infusion of 0.05 mg/kg per minute for the next 4 minutes. Depending on the desired ventricular response, the maintenance infusion may then be continued at 0.05 mg/kg per minute or increased stepwise (e.g., by 0.1 mg/kg per minute increments to a maximum of 0.2 mg/kg per minute), with each step being maintained for ≥4 minutes. |

*IV*, Intravenous; *q*, every.

# Case 2

A 8 y/o boy with w:45 kg, ht:120, BP: 150/100, acanthosis nigricans, sever weakness
Bone age:6, random BS:188, Na and K: normal
DXA scan osteoporosis (Zscore -4) with compression fractures in L3,4

1)What is your diagnosis?
2)What is your management plans?
3)What is your treatment comment?

## TABLE 15.10 Classification of Causes of Cushing Syndrome

### ACTH-Dependent Causes

Cushing disease (pituitary dependent)
Ectopic ACTH syndrome
Ectopic CRH syndrome
Macronodular adrenal hyperplasia
Iatrogenic (treatment with [1-24]ACTH)

### ACTH-Independent Causes

Adrenal adenoma and carcinoma
Primary pigmented nodular adrenal hyperplasia and Carney syndrome
McCune-Albright syndrome
Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β)
Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)

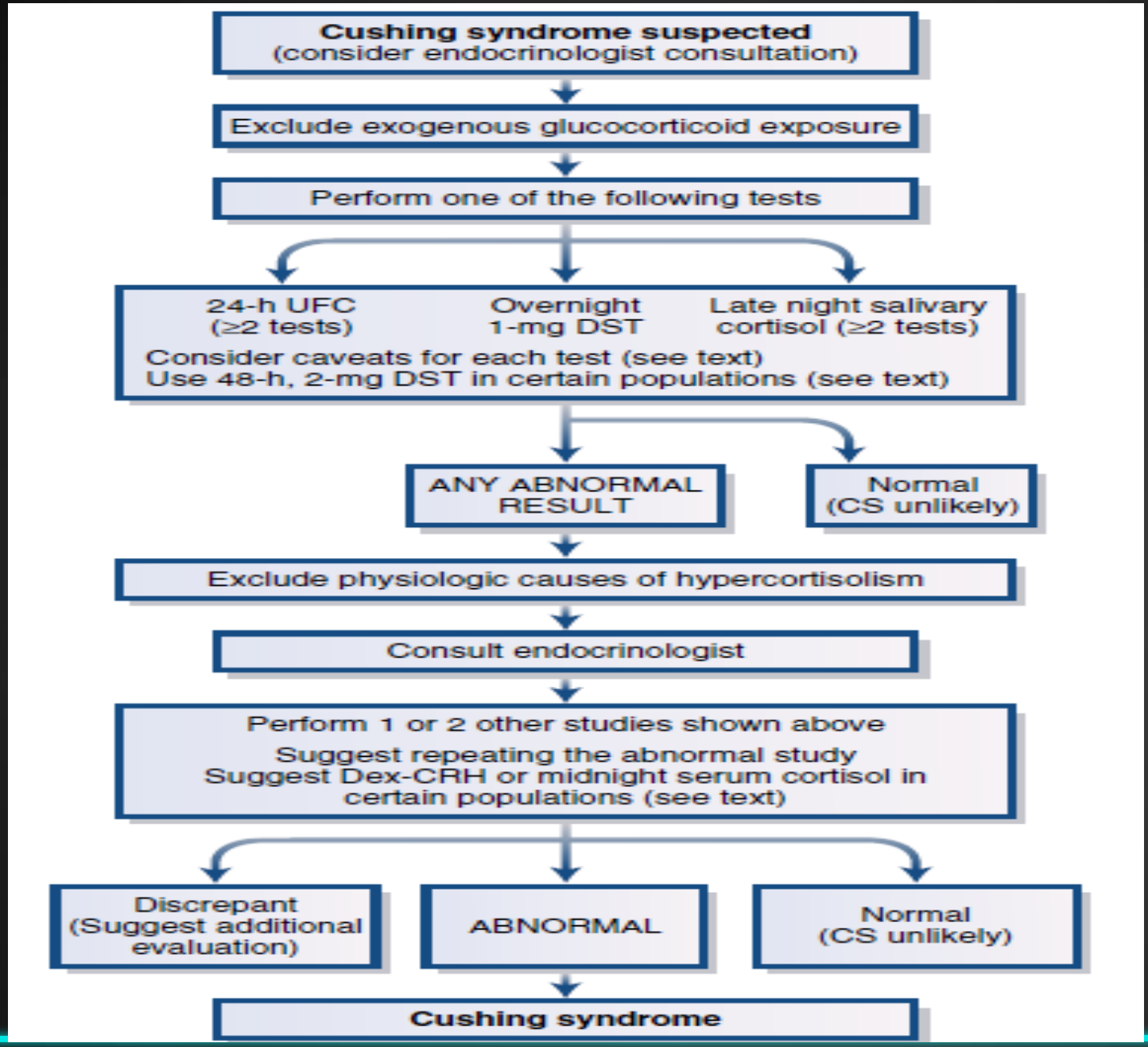
### Other Causes of Hypercortisolism (non-neoplastic)

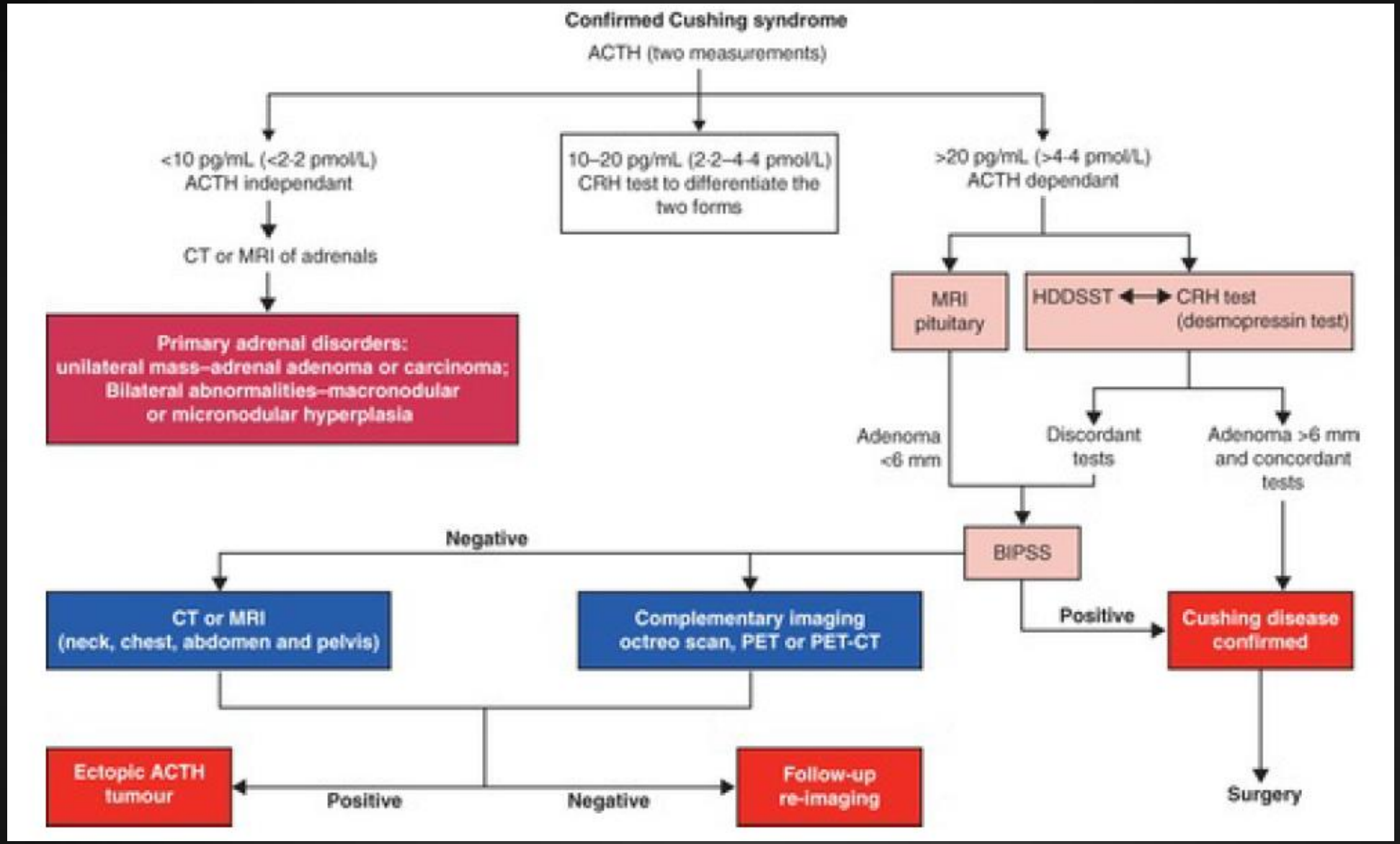
Alcoholism
Depression
Obesity
Pregnancy

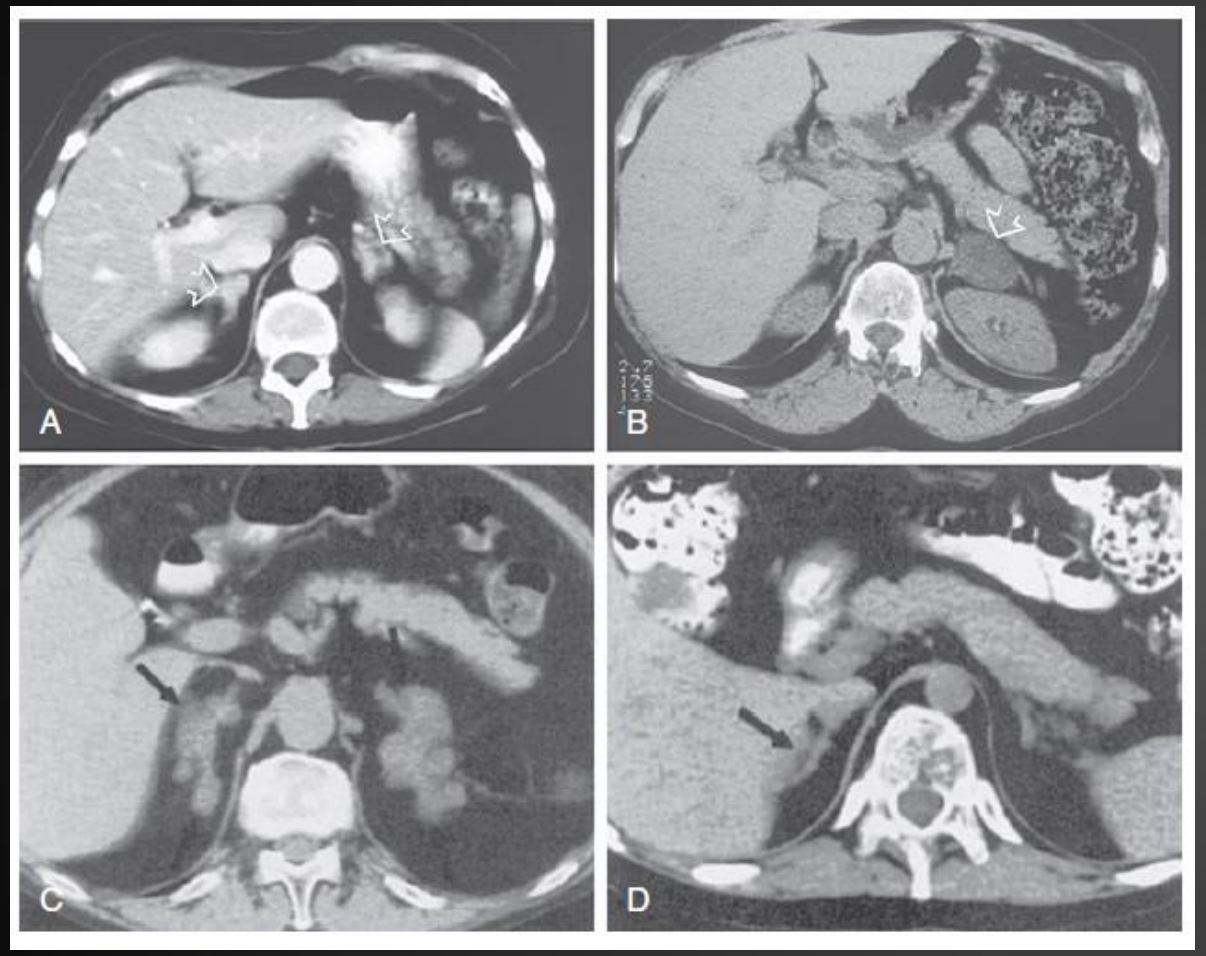
Hypertension occurs in 75% to 80% of patients with Cushing syndrome:
increased production of DOC
endogenous vasoconstrictors (e.g., epinephrine, angiotensin II)
increased cardiac output
activation of the RAA system by increased hepatic production of angiotensinogen
cortisol activation of the mineralocorticoid receptor

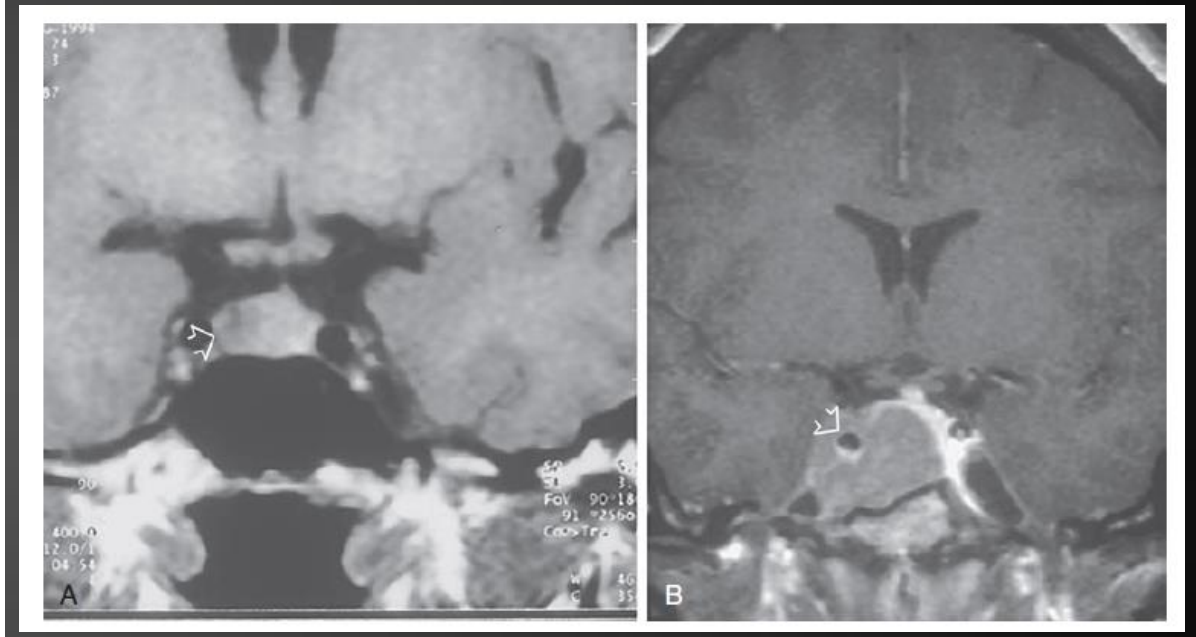
## TABLE 15.9 Symptoms and Signs for the Diagnosis of Cushing Syndrome

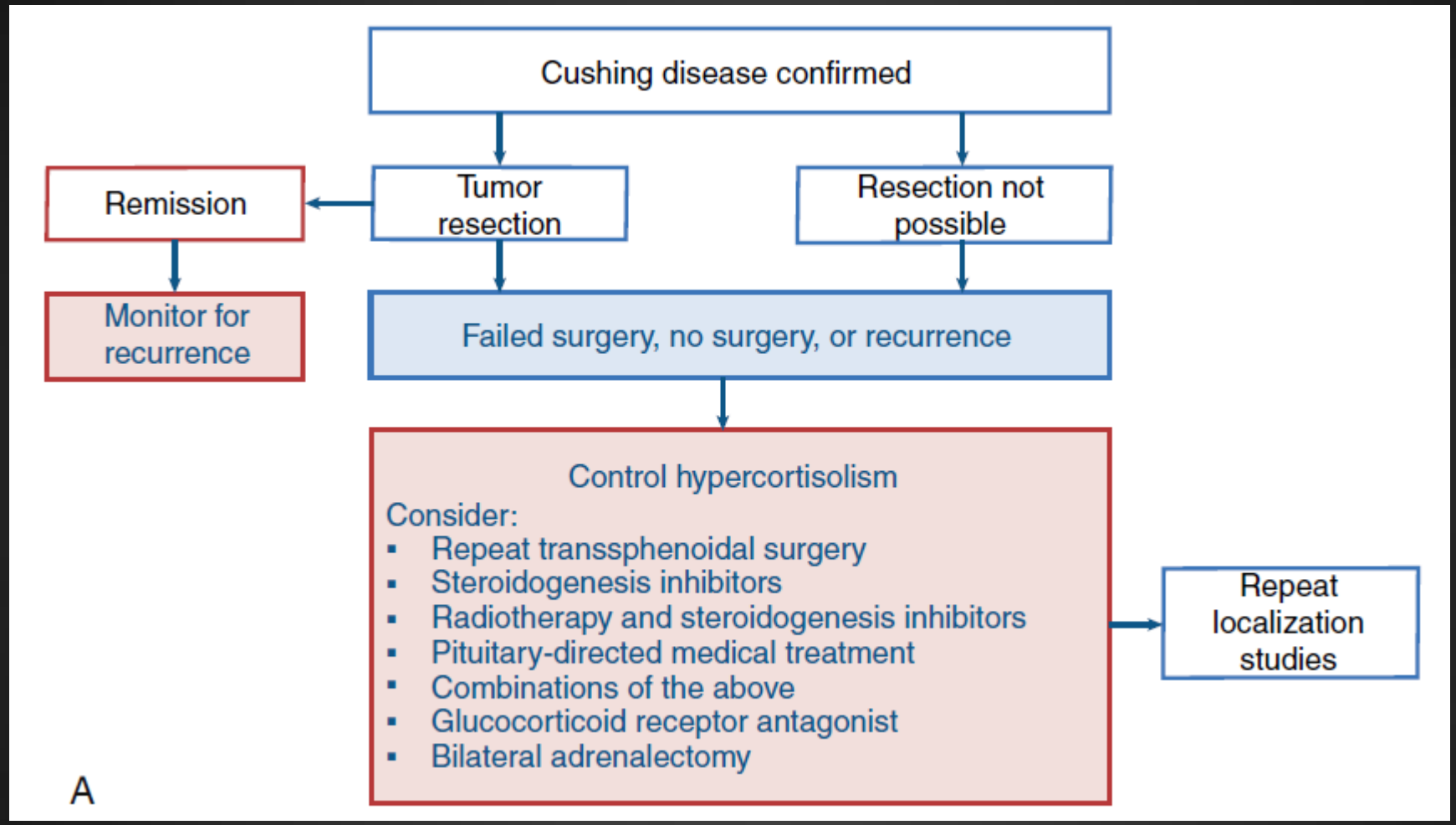
| Discriminatory | Less Discriminatory |
|---|---|
| Signs<br>• Facial plethora<br>• Proximal myopathy<br>• Cutaneous striae (red-purple, >1 cm wide)<br>• Bruising<br>• In children—weight gain with reduced height percentile | Signs<br>• Central obesity<br>• Buffalo hump, supraclavicular fullness<br>• Facial fullness<br>• Acne and hirsutism<br>• Skin thinning<br>• Poor wound healing<br>• Peripheral edema |
| Symptoms and complications (especially at a young age)<br>• Hypertension<br>• Diabetes mellitus<br>• Osteoporosis and vertebral fractures | Symptoms and complications<br>• Fatigue<br>• Weight gain<br>• Depression, mood and appetite change, impairment of concentration and memory<br>• Back pain<br>• Oligomenorrhea, polycystic ovary syndrome<br>• Recurrent infections<br>• Kidney stones |


Cushing syndrome suspected
(consider endocrinologist consultation)
Exclude exogenous glucocorticoid exposure
Perform one of the following tests
24-h UFC
(≥2 tests)
Overnight
1-mg DST
Late night salivary
cortisol (≥2 tests)
Consider caveats for each test (see text)
Use 48-h, 2-mg DST in certain populations (see text)
ANY ABNORMAL
RESULT
Normal
(CS unlikely)
Exclude physiologic causes of hypercortisolism
Consult endocrinologist
Perform 1 or 2 other studies shown above
Suggest repeating the abnormal study
Suggest Dex-CRH or midnight serum cortisol in
certain populations (see text)
Discrepant
(Suggest additional
evaluation)
ABNORMAL
Normal
(CS unlikely)
Cushing syndrome


Confirmed Cushing syndrome
ACTH (two measurements)
<10 pg/mL (<2·2 pmol/L)
ACTH independant
10–20 pg/mL (2·2–4·4 pmol/L)
CRH test to differentiate the two forms
>20 pg/mL (>4·4 pmol/L)
ACTH dependant
CT or MRI of adrenals
Primary adrenal disorders:
unilateral mass–adrenal adenoma or carcinoma;
Bilateral abnormalities–macronodular or micronodular hyperplasia
MRI pituitary
HDDSST
CRH test (desmopressin test)
Adenoma <6 mm
Discordant tests
Adenoma >6 mm and concordant tests
BIPSS
Negative
Positive
CT or MRI
(neck, chest, abdomen and pelvis)
Complementary imaging
octreo scan, PET or PET-CT
Cushing disease confirmed
Ectopic ACTH tumour
Positive
Negative
Follow-up re-imaging
Surgery


A
B
C
D

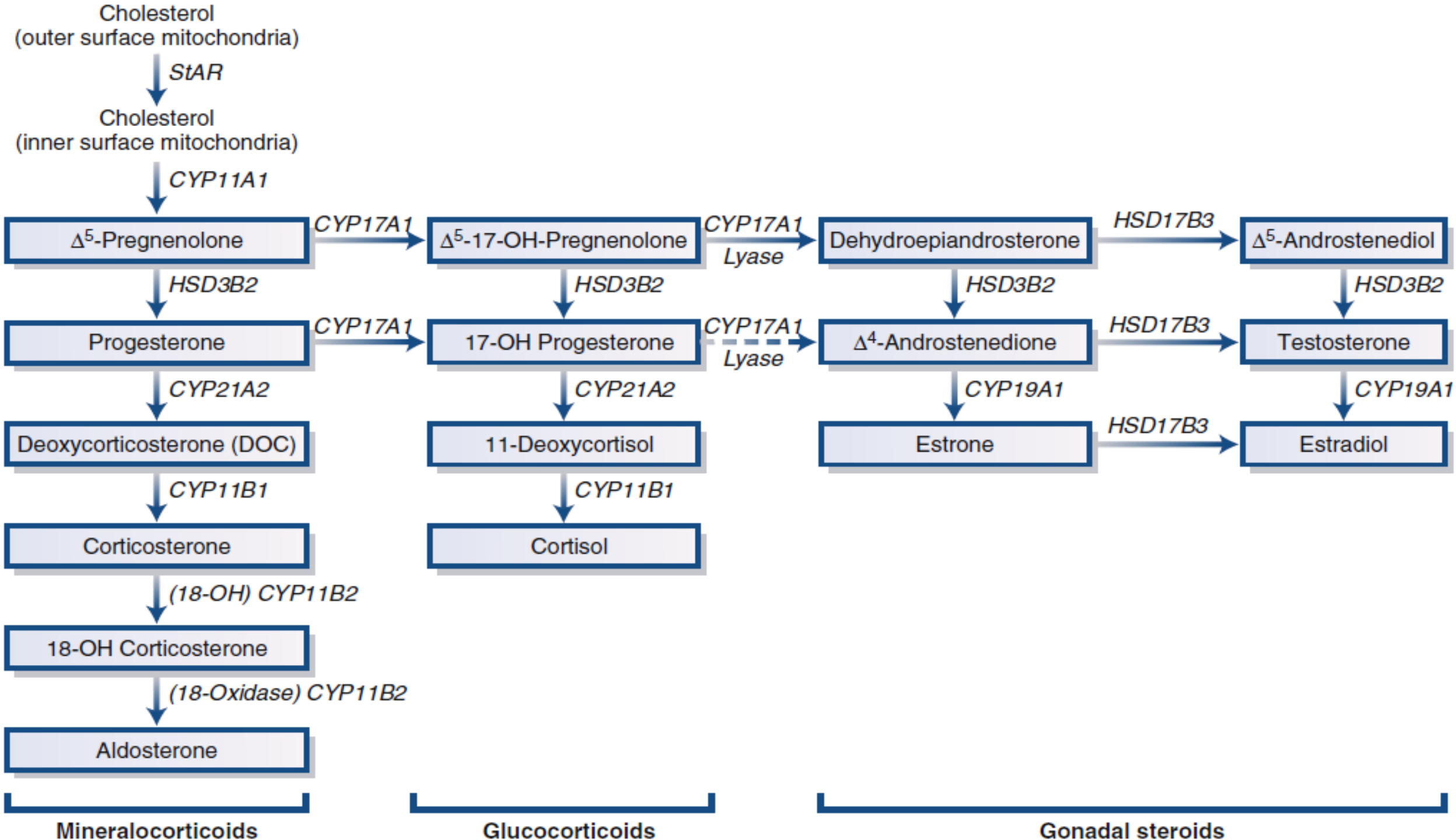

A
B


Cushing disease confirmed
Tumor resection
Remission
Resection not possible
Monitor for recurrence
Failed surgery, no surgery, or recurrence
Control hypercortisolism
Consider:
Repeat transsphenoidal surgery
Steroidogenesis inhibitors
Radiotherapy and steroidogenesis inhibitors
Pituitary-directed medical treatment
Combinations of the above
Glucocorticoid receptor antagonist
Bilateral adrenalectomy
Repeat localization studies
A

# Case 3

18 Y/O Female with primary amenorrhea is referred.
Ph/E: breast stage 4, without pubic and axillary hair, unilateral inguinal hernia and BP:160/110, height: 180, BA:14 y
Lab data :increased LH and FSH, decreased plasma renin activity, hypokalemic alkalosis

What is the cause of amenorrhea in the patient?
What is your plan for the management in this situation?


Cholesterol
(outer surface mitochondria)
StAR
Cholesterol
(inner surface mitochondria)
CYP11A1
Δ5-Pregnenolone
CYP17A1
Δ5-17-OH-Pregnenolone
CYP17A1
Lyase
Dehydroepiandrosterone
HSD17B3
Δ5-Androstenediol
HSD3B2
HSD3B2
HSD3B2
Progesterone
CYP17A1
17-OH Progesterone
CYP17A1
Lyase
Δ4-Androstenedione
HSD17B3
Testosterone
CYP21A2
CYP21A2
CYP19A1
CYP19A1
Deoxycorticosterone (DOC)
11-Deoxycortisol
Estrone
HSD17B3
Estradiol
CYP11B1
CYP11B1
Corticosterone
Cortisol
(18-OH) CYP11B2
18-OH Corticosterone
(18-Oxidase) CYP11B2
Aldosterone
Mineralocorticoids
Glucocorticoids
Gonadal steroids

# Combined CYP17 Deficiency

**TABLE 24.11 Clinical Features of Combined CYP17 Deficiency in 46,XY Individuals**

| | |
|---|---|
| Karyotype | 46,XY |
| Inheritance | Autosomal recessive; mutations in *CYP17* gene |
| Genitalia | Female, ambiguous, or hypospadias |
| Wolffian duct derivatives | Absent or hypoplastic |
| Müllerian duct derivatives | Absent |
| Gonads | Testes |
| Physiologic features | Absent or poor virilization at puberty, gynecomastia, hypertension |
| Hormone profile | Decreased T; increased LH and FSH; increased plasma deoxycorticosterone, corticosterone, and progesterone; decreased plasma renin activity<br>Low renin hypertension with hypokalemic alkalosis |

*CYP17*, 17α-Hydroxylase/17,20-lyase; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *T*, testosterone.

**TABLE 24.12 Clinical Features of Isolated 17,20-Lyase Deficiency in 46,XY Individuals**

| | |
|---|---|
| Karyotype | 46,XY |
| Inheritance | Autosomal recessive; mutations in *CYP17* gene, usually affecting key redox domains |
| Genitalia | Female, ambiguous, or hypospadias |
| Wolffian duct derivatives | Absent or hypoplastic |
| Müllerian duct derivatives | Absent |
| Gonads | Testes |
| Physiologic features | Absent or poor virilization at puberty; gynecomastia |
| Hormone profile | Decreased plasma T, DHEA, androstenedione, and estradiol; abnormal increase in plasma 17-hydroxyprogesterone and 17-hydroxypregnenolone; increased LH and FSH; increased ratio of C21 deoxysteroids to C19 steroids (DHEA, androstenedione) after hCG stimulation |

*CYP17*, 17α-Hydroxylase/17,20-lyase; *DHEA*, dehydroepiandrosterone; *FSH*, follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone; *T*, testosterone.

# Therapeutic Measures

Glucocorticoid administration+ calcium-channel blockers or potassium-sparing diuretics

Surgical correction of genitalia

sex steroid replacement
in male pseudohermaphroditism consistent with sex of rearing
Estrogen replacement in female at 12 years
Testosterone replacement if reared as male (rare)

# Case 4

A 16 y/o girl with virilizing features such as secondary amenorrhea, hirsutism, acne, cliteromegaly and HTN
Lab: hypokalemic alkalosis, Elevated serum cortisol concentrations and increased 24-hr urinary free cortisol excretion in the absence of Cushing syndrome. ACTH  serum levle is NL. androstenedione, DHEA and deoxycorticosterone are elevated.

What is your diagnosis?
What is your treatment?

# Generalized Glucocorticoid Resistance

mutations in the **glucocorticoid receptor** (encoded by the *NR3C1* gene)
Adrenal hyperplasia with increased production of adrenal steroids with mineralocorticoid activity including cortisol, deoxycorticosterone, and corticosterone, and also androgens and precursors, including androstenedione, DHEA, and DHEA sulfate.
The high cortisol concentrations do not cause Cushing syndrome.
Chronic fatigue and occasional anxiety, hypertension and hypokalemic alkalosis

The increased concentrations of adrenal androgens may cause ambiguous genitalia in females and gonadotropin independent precocious puberty in children of either gender; acne; hirsutism, and infertility in both sexes; menstrual irregularities in females; and oligospermia in males.
Testicular adrenal rest tumors and ACTH-secreting pituitary adenomas occasionally occur.
Lab: Elevated serum cortisol concentrations and increased 24-hr urinary free cortisol excretion in the absence of Cushing syndrome. ACTH may be normal or high. circadian pattern of ACTH and cortisol secretion is preserved, although at higher-than-normal concentrations, and there is resistance of the HPA axis to dexamethasone suppression.
Tx: The goal of treatment is to suppress the excess secretion of ACTH (dexamethasone (typically ~20-40 µg/kg/day)

# CASE 5

A 6 y/o boy with FTT , **nephrogenic DI(**polyuria and polydipsia, **nephrocalcinosis)** , BP:200/120
PMH: IUGR
Lab: Hypokalemic alkalosis, Sodium levels in ULN
Serum cortisol and ACTH levels are normal
KUB sono: **nephrocalcinosis**
**Echo cardiography: LVH**

**What is your diagnosis?**
**What is your treatment?**

# Apparent Mineralocorticoid Excess

mutations in the *HSD11B2*
cortisol is able to efficiently occupy the mineralocorticoid receptor
**Licorice and** Carbenoxolone.

in childhood with hypertension, hypokalemia, intrauterine growth restriction, failure to thrive, hypertension, polyuria and polydipsia, and poor growth.
Severe hypertension (to ~200/120 mm Hg) is almost always present or paroxysmal
Hypokalemic alkalosis can eventually cause **nephrocalcinosis** (often visible on renal ultrasound) and **nephrogenic diabetes insipidus** leading to polyuria and polydipsia.
**Rhabdomyolysis and rising CPK.**

# LABORATORY FINDING

Aldosterone and renin levels are very low

Hypokalemic alkalosis, Sodium levels in ULN

Serum cortisol and ACTH levels are generally within normal limits

urinary ratio of free cortisol to free cortisone is elevated

# Treatment

low-salt diet

potassium supplementation

spironolactone or eplerenone
amiloride or triamterene

Dexamethasone in practice it is much less effective

# Hyperthyroidism

activity and sensitivity to circulating catecholamines increase.
tachycardia, high cardiac output,
increased stroke volume, decreased peripheral vascular resistance,
increased systolic blood pressure

TX: β-adrenergic blocker

# Hypothyroidism

hypertension (usually diastolic) IN 30% OF affected patients

increased systemic vascular resistance and extracellular volume expansion

# Acromegaly

in 20% to 40% of the patients with acromegaly and is associated with sodium retention and extracellular volume expansion.

The hypertension of acromegaly most effectively by curing the excess of growth hormone: surgery or medication(pegvisomant, somatostatin analogs).

Residual hypertension can be treated with diuretic therapy.

# thanks for your attention