Board Review 30June2016: Cortisol deficiency - Cortisol excess
Anna Isfort

2. Pathology

A. Cortisol deficiency

1. Pathophysiology

A. Understand the recovery of the HPA axis after chronic suppression with exogenous glucocorticoids

Synthetic corticosteroids suppress the function of the HPA axis, degree of suppression depends on the dose and duration of treatment. Can occur from use of oral, topical, or inhaled preparations. Sudden cessation of corticosteroid therapy can result in adrenal failure. This may also occur after treatment with high doses of the synthetic progesterone, medroxyprogesterone acetate, which possesses glucocorticoid agonist activity. Among patients taking any steroid dose for less than 3 weeks duration, clinically significant suppression of the HPA axis is rarely a problem. Recovery of HPA axis can be seen within 6 weeks in about 1/2 of patients, and within 6 months in most subjects, however up to 10% of patients still have biochemical evidence of hypoadrenalism 6-20mos after GC withdrawal.

Relative GC potencies (oral/parenteral formulations):
20mg hydrocortisone = 5mg prednisolone/prednisone = 0.75mg dexamethasone

Inhaled steroids: budesonide more potent action at glucocorticoid receptor than dexamethasone – degree of action at GC receptor depends on systemic absorption. Fluticasone more frequently associated with adrenal suppression at high doses than budesonide or beclomethasone.

B. Recognize the possibility of isolated ACTH deficiency

Recessive mutations in the T-box factor TPIT (TBX19) have been identified in patients with severe early onset isolated ACTH deficiency with profound hypoglycemia, prolonged jaundice, and sudden neonatal death. TPIT is a transcription factor involved in the differentiation of corticotrophs and regulates POMC expression.

Mutation in PCSK1 gene = Defect in post-translational processing of POMC to ACTH by prohormone convertases PC1 and PC2 - general defects in peptide processing = ACTH deficiency, also have DM (defective cleavage of proinsulin to insulin).

POMC gene mutation: defective synthesis of ACTH = ACTH deficiency, red hair, severe obesity

C. Know the clinical characteristics, inheritance, and genetic etiology of ACTH unresponsiveness syndromes

ACTH receptor defect = familial glucocortidoid deficiency (FGD) type1 - inactivating mutation of melanocortin 2 receptor (MC2R). AR inheritance, present in childhood with neonatal hypoglycemia,
or later with increasing pigmentation. Intact RAA system. High ACTH, low cortisol, normal renin/aldo.

- MC2R accessory protein defect = FGD type 2 - mutation in MRAP gene
- Triple-A syndrome = alacrima, achalasia, Addisonism. Also called Allgrove syndrome, caused by defects in ALADIN/AAAS gene.
- These disorders are characterized by isolated glucocorticoid deficiency, hyperpigmentation, and markedly elevated ACTH. 15% of individuals with triple-A syndrome have evidence of mineralocorticoid insufficiency, those with the most severe LOF manifesting with hyponatremia on presentation.

D. Know that adrenal insufficiency can result from adrenal hemorrhage

Risk factors for adrenal hemorrhage: prolonged labor, birth trauma, LGA, Beckwith-Weidemann syndrome, heparin induced thrombocytopenia (HIT), sepsis (specifically with Pseudomonas infection, and meningococcemia = Waterhouse-Friderichsen syndrome)

E. Understand the hypothalamic pituitary abnormalities that can cause secondary adrenocortical insufficiency


Pituitary: congenital aplasia/hypoplasia, tumor (craniopharyngioma), tumor treatment, hypophysitis, apoplexy
- Gene mutations affecting pituitary development: HESX1, LHX4, SOX3, PROP1 - all may have ACTH deficiency that may develop over time (see below).

F. Know the association of hypoadrenalism with adrenoleukodystrophy and related disorders

Adrenoleukodystrophy - inherited (X-linked recessive) demyelinating disorder due to failure of peroxisomal B-oxidation of FA = accumulation of VLCFA. Mutation in ABCD1 gene (chr Xq28).
- Several forms: childhood cerebral form (40% of cases), adult adrenomyeloneuropathy (40%), and Addison disease (7%).
- Degree of adrenal insufficiency does not correlate with neurologic status

Other metabolic disorders:
Zellweger syndrome - peroxisome biogenesis disorder
Smith-Lemli-Opitz syndrome - disorder of cholesterol synthesis
Wolman syndrome – disorder of cholesterol metabolism with abnormal accumulation of mucolipids and mucopolysaccharides in tissues (to include adrenals)
Kearn-Sayres syndrome (mitochondrial myopathy) and other mitochondrial disorders

G. Know that adrenal insufficiency may occur in AIDS

In advanced HIV, adrenal gland is infected, can lead to dysfunction. Opportunistic infections related to HIV can also infect adrenal glands OR can cause hypophysitis or hypothalamic dysfunction: TB, CMV, cryptococcus, nocardia, MAI
Secondary malignancies can affect adrenals: Kaposi sarcoma, lymphoma
Drugs used for HIV or opportunistic infections can suppress adrenal function:
- ketoconazole used for fungal infections = blocks adrenal steroid synthesis
- rifampin alters glucocorticoid metabolism
- megesterol used for appetite stimulation can lead to adrenal insufficiency
- Chronic steroids can suppress HPA axis

H. Know that adrenal hypoplasia congenita may be due to an X-linked DAX-1 (NROB1) gene mutation and may be associated with hypogonadotropic hypogonadism

Clinical features: male with adrenal insufficiency and hypogonadotropic hypogonadism, in severe types may have mineralocorticoid deficiency, glucocorticoid deficiency may be of late onset and minipuberty of infancy is often normal.

DAX1 (NROB1) = nuclear receptor expressed in adrenal cortex, gonads, and hypothalamus, mediates differentiation of fetal adrenal-gonadal primordium into adrenals and gonads

I. Know that congenital adrenal hypoplasia may be part of an x-linked contiguous gene deletion associated with glycerol kinase deficiency, retardation, and muscular dystrophy

Deletion of multiple genes on chromosome Xp21 including DAX1 gene.

J. Understand that adrenal cortical insufficiency may result from congenital adrenal hypoplasia or hyperplasia of various etiologies.

See later discussion of CAH.

K. Understand that adrenal hypofunction (cortisol deficiency) may occur after high dose glucocorticoid therapy for as little as 2-3 weeks, and understand symptoms and signs of glucocorticoid withdrawal

Glucocorticoids suppress secretion of CRH by hypothalamus, and ACTH by pituitary = secondary adrenal cortical atrophy - this finding is expected with higher dose and longer term therapies. Symptoms of glucocorticoid withdrawal are the same as AI - anorexia, nausea, weight loss, arthralgia, lethargy, postural dizziness, fatigue, weakness

L. Know that adrenocortical insufficiency may occur after removal of adrenal or ACTH secreting pituitary tumors

Due to HPA axis suppression by high ACTH and/or cortisol concentrations and atrophy of normal adrenal tissue (in the case of adrenal tumor).

M. Know that certain chemotherapeutic agents may cause adrenal insufficiency

Ketoconazole and to lesser extent fluconazole - inhibit cortisol synthesis
Etomidate -inhibits cortisol synthesis
Mitotane - adrenocorticolytic - used to treat adrenal tumors and in medical management of Cushing syndrome
Metyrapone - inhibits 11B-hydroxylase conversion of 11-deoxycortisol to cortisol
Suramin - antiparasite drug and used to treat prostate cancer

Drugs that increase cortisol metabolism (but no effect on steroid biosynthesis): phenytoin, barbiturates, rifampin, rHGH, levothyroxine.

Drugs that suppress HPA axis: glucocorticoids, megestrol acetate, opioids

**N. Know which single gene defects cause hypopituitarism that includes ACTH deficiency**

PROP1 - chromosome 5q, AR inheritance. Transcription factor required for pituitary development and POU1F1 activation. Clinical features = hypopit with deficient GH, PRL, TSH and may have insufficient FSH, LH, ACTH.

HESX1 - chromosome 3p21.2, AR inheritance. Transcription factor required for pituitary development, expressed in Rathkes pouch, mutation is commonly seen in septo-optic dysplasia. Deficiency of GH, PRL, TSH, LH, FSH, ACTH, and may have posterior pituitary defects.

LHX4 - chromosome 1q25, AD inheritance. Transcription factor required for activation of PROP1 and POU1F1. Deficiency of GH, TSH, ACTH. Contrast to LHX3 mutation - hypopit but with intact ACTH.

SOX3 - chromosome Xq27, X-linked recessive. Deficiency of GH, TSH, ACTH, FSH, LH + intellectual disability.

**2. Clinical implications**

**A. Know that the anti-inflammatory potency of glucocorticoids may differ from their capacity to suppress the HPA axis**

Williams - Table 15-7: Relative Biologic Potencies of Synthetic steroids

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Anti-inflammatory Action</th>
<th>HPA Suppression</th>
<th>Salt Retention</th>
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</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3</td>
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<td>0.75</td>
</tr>
<tr>
<td>Prednisolone</td>
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<td>Methylprednisolone</td>
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<tr>
<td>Fludrocortisone</td>
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<td>12</td>
<td>125</td>
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<tr>
<td>Δ 1 Fludrocortisone</td>
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<td>—</td>
<td>225</td>
</tr>
<tr>
<td>Triamcinolone</td>
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<td>0</td>
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<tr>
<td>Dexamethasone</td>
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<td>17</td>
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Harriet Lane:

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Relative GC Effect</th>
<th>MC Effect</th>
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<tr>
<td>Hydrocortisone</td>
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<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4x</td>
<td>0.25x</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4x</td>
<td>0.25x</td>
</tr>
<tr>
<td>Methylprednisolone</td>
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</tr>
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<td>Dexamethasone</td>
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<td>No effect</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>15x</td>
<td>200x</td>
</tr>
</tbody>
</table>
B. Understand the diagnosis and lab evaluation of decreased adrenal cortical function

Primary hypoadrenalism = glucocorticoid deficiency in the setting of adrenal disease AND mineralocorticoid deficiency
Secondary hypoadrenalism = ACTH deficiency (causing cortisol deficiency), with intact RAA system

Clinical symptoms of adrenal insufficiency: anorexia, nausea, weight loss, arthralgia, lethargy, postural dizziness, weakness, fatigue, hypotension, hyperpigmentation if primary AI, azotemia, anemia

Lab findings:
- Primary adrenal insufficiency: Hyponatremia, hyperkalemia, hypoglycemia, elevated PRA and low or low-normal plasma aldosterone, low plasma cortisol (morning sample), low DHEAS may be seen, elevated ACTH
- Secondary adrenal insufficiency: hypoglycemia, low plasma cortisol, low ACTH

Morning cortisol <3 mcg/dL = diagnostic of AI, confirm with ACTH stimulation test.

ACTH stimulation tests:
- High dose - give 250mcg (or 15mcg/kg) ACTH(1-24) IM or IV, measure plasma cortisol at baseline, 30, and 60 minutes.
  - Normal response = peak plasma cortisol >18 mcg/dL at 30min, > 20mcg/dL at 60min.
  - Useful to differentiate between primary and secondary AI (primary = insufficient response, secondary = adequate response of adrenals to ACTH stimulation)
  - May miss mild adrenal insufficiency with large dose ACTH
  - Used to evaluate for enzyme deficiency in CAH
- Low dose - give 1mcg ACTH(1-24) IM or IV, measure plasma cortisol at baseline, 30 and 60 minutes
  - More sensitive than 250mcg test (fewer false negatives)
  - Prone to technical error in medication administration - must dilute 250mcg vial in 250mL saline, and give 1mL

Other stimulation tests:
- Insulin tolerance test (gold standard): give 0.1 - 0.15 units/kg insulin IV, measure plasma cortisol at 0, 30, 45, 60, 90, 120 minutes. Adequate hypoglycemia <40 mg/dL required. Should see peak plasma cortisol >18 mcg/dL.
- Overnight metyrapone test: give 30mg/kg metyrapone at midnight, measure cortisol, 11DOC and ACTH at 8am the following morning.
  - If HPA axis intact - should see elevated ACTH, peak 11DOC >7mcg/dL, cortisol <5 mcg/dL
  - High basal ACTH and/or high ACTH after metyrapone suggest primary AI
- CRH stimulation test: give 1mcg/kg CRH IV with measurement of ACTH and cortisol every 15min x 2h.
  - Primary AI - elevated ACTH at baseline with further ACTH elevation, minimal change in cortisol
  - Secondary AI - low ACTH with no response to CRH
  - Hypothalamic etiology of AI - steady rise in ACTH and cortisol

Other labs to consider: 21-hydroxylase antibodies, VLCFA if ALD is suspected, CAH panel
C. Understand the cause of hyperpigmentation in primary glucocorticoid deficiency

Caused by increased stimulation of melanocortin 1 receptor (MC1R) by ACTH, not necessarily by increased a-MSH produced during cleavage of POMC to produce more ACTH.

D. Know the mild increase in serum TSH present in adrenal insufficiency

Cortisol suppressed TSH secretion and inhibits conversion of T4 to T3, so if deficient, there is relative TSH increase and increase in conversion of T4 to T3.

E. Plan replacement therapy for hypoadrenocorticism with glucocorticoids and mineralocorticoids as indicated

GC replacement:
- Hydrocortisone: 10-15 mg/m2/day HC divided into 2-3 daily doses in adults, 8-12 mg/m2/day in children (may give higher doses in the morning to mimic normal physiology).

MC replacement:
- Fludrocortisone 0.05 - 0.2 mg/day (usually 0.1mg/day)
- Infants may require higher dosing

NaCl supplements: 1-3 g/day = 8-10 mEq/kg/d div QID for 6-12mos until eating more sodium in diet.
F. Understand that aldosterone secretion can be normal in secondary adrenal deficiency

G. Understand the clinical and lab features of cortisol resistance

Rare, sporadic or familial, partial insensitivity to glucocorticoids due to glucocorticoid receptor gene mutation. Impaired glucocorticoid feedback = increased CRH, ACTH, AVP, cortisol, mineralocorticoids, and androgens.

Labs: high ACTH, cortisol, aldosterone, androgens

Clinical features: NO signs/sx of cortisol excess. + signs of mineralocorticoid excess: hypertension, hypokalemic alkalosis. + signs of androgen excess: clitoromegaly, precocious puberty, short stature, hirsutism, impaired fertility, normal or increased BMD.

Treatment: dexamethasone to suppress ACTH (which will decrease serum cortisol), decrease adrenal androgens and decrease mineralocorticoid receptor activation by excess cortisol, may require high dose dexamethasone.

*Note the difference between cortisol resistance (GC receptor defect, high ACTH and cortisol) and familial glucocorticoid deficiency (ACTH receptor defect, high ACTH, low cortisol)

H. Distinguish the key features of late onset and virilizing classic and non-classic CAH

Late onset CAH - presentation in childhood or adulthood with features of hyperandrogenism (acne, premature pubarche, clitoromegaly, hirsutism, menstrual irregularity, infertility), or mild bone age advancement.
- May be misdiagnosed in females as PCOS.
- No clinically significant cortisol or mineralocorticoid deficiency, however up to 30% of adult patients may have impaired response to ACTH stim test and may be prone to stress induced adrenal insufficiency.
- Mild 17-OHP elevation. May not require treatment, or may use antiandrogens or glucocorticoids for sx of hyperandrogenism

Simple virilizing CAH: 21 hydroxylase deficiency: females appear virilized at birth with clitoromegaly, may have labial fusion and spectrum of genital ambiguity, and boys with early onset of virilization with prepubertal testicular volumes and females in childhood with precocious puberty (aka precocious pseudopuberty), some growth acceleration.
- Some degree of mineralocorticoid and glucocorticoid deficiency but without frank AI or salt wasting.
- 17-OHP moderately elevated, treat with mineralocorticoid and glucocorticoids

Classic salt wasting CAH: females with ambiguous genitalia at birth, males present with salt wasting crisis at 7-10 DOL.
- 17-OHP markedly elevated
- Treat with glucocorticoid, mineralocorticoid, salt

- 1gm salt = 17mEq Na. 1tsp = 6gm salt. 1tsp = 102 mEq Na
I. Understand the risk to a patient or relative of a patient of having a child affected with CAH

For the most common classic CAH 21-hydroxylase deficiency - Autosomal recessive inheritance, incidence 1:10000 - 1:15000, carriers 1:60. In some populations more common - alaskan inuit 1:300.

Nonclassic CAH more common: 1:500 - 1:1000

For patients - all children of patients will be carriers. If partner is carrier - 50% of offspring will be carriers, 50% will have CAH, and clinical features will depend on mutations present.

For relatives of patients - if your child has CAH, you are a carrier, or have CAH. If your sibling has CAH and both parents are carriers, 25% chance you have CAH, 50% you are carrier, 25% chance you are unaffected.

J. Understand the concept of prenatal diagnosis of CAH

Performed by screening for gene mutation in high risk individuals, sample obtained via CVS or amniocentesis. If positive, and female fetus, dexamethasone may be used to prevent virilization, most effective if started early as virilization starts as early as 6 weeks post-conception.

- Dex crosses placenta and is not inactivated by placental 11B-HSD, suppresses fetal androgen production to prevent virilization.
- Treatment must be started before confirmation of disease or gender – so 7/8 treated patients will not be affected females, and treatment will be discontinued.

K. Understand the medical and surgical management of the different forms of CAH

Medical management = glucocorticoid and mineralocorticoid replacement (see above), NaCl supplementation, antiandrogen therapy for women as needed, fertility assistance as needed

Surgical management = genital reconstruction if needed, bilateral adrenalectomy as last resort.

L. Understand that girls with virilizing classic CAH may have certain play preferences and behaviors

Females may prefer more male-typical play behaviors than unaffected sisters, however gender identity remains female.
M. Know the expected internal genital structures in girls with virilizing classic CAH

Normal internal female genital structures - normal uterus, fallopian tubes, ovaries.

N. Understand the signs and symptoms of GC deficiency

Anorexia, nausea/vomiting, fatigue, weakness, lethargy, postural hypotension, weight loss, hyperkalemia, hyponatremia, hypoglycemia.

O. Understand the management of cortisol deficiency at times of increased stress

Stress dosing of hydrocortisone is required:
- Increase oral glucocorticoid dose 3 fold (10 mg/m2 TID instead of 10mg/m2 q24h)
- In case of po intolerance, give hydrocortisone IM dose: 50mg/m2 and seek emergency care
- For planned procedures:
  - Minor procedure: hydrocortisone 50mg/m2 x1 IV, followed by oral stress dosing as above x 24h or until back to medical baseline
  - More significant surgery, trauma, or severe stress: hydrocortisone 100mg/m2 x1 IV, followed by 25mg/m2 q6h x 24h, followed by oral or IV stress dosing of 3x maintenance dose until back to medical baseline. Replete electrolytes and treat hypotension as needed.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Suggested Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home management of illness with fever</td>
<td>Hydrocortisone replacement doses doubled (&gt;38°C) or tripled (&gt;39°C) until recovery; Adults, im or sc hydrocortisone 100 mg; children, im hydrocortisone 50 mg/m² or estimate; infants, 25 mg; school-age children, 50 mg; adolescents, 100 mg.</td>
</tr>
<tr>
<td>Unable to tolerate oral medication due to gastroenteritis or trauma</td>
<td>Hydrocortisone, 25–75 mg/24h (usually 1 to 2 d); Children, im hydrocortisone 50 mg/m² or hydrocortisone replacement doses doubled or tripled.</td>
</tr>
<tr>
<td>Minor to moderate surgical stress</td>
<td>Hydrocortisone, 100 mg per iv injection followed by continuous iv infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h iv or im).</td>
</tr>
<tr>
<td>Major surgery with general anesthesia, trauma, delivery, or disease that requires intensive care</td>
<td>Children, hydrocortisone 50 mg/m² iv followed by hydrocortisone 50–100 mg/m²/d divided q 6h</td>
</tr>
<tr>
<td>Acute adrenal crisis</td>
<td>Weight-appropriate continuous iv fluids with 5% dextrose and 0.2 or 0.45% NaCl. Rapid tapering and switch to oral regimen depending on clinical state.</td>
</tr>
</tbody>
</table>

P. Know the differential diagnosis of adrenal calcification

Infection: TB, histoplasmosis
Tumor: adenoma, carcinoma, pheochromocytoma, neuroblastoma, adrenal cyst, hemangioma
Hemorrhage, or post-hemorrhagic finding
Wolman disease: Deficiency of lysosomal acid lipase, infiltration of organs by macrophages

Q. Know that adrenoleukodystrophy is an x-linked condition associated with increases of C22-C26 VLCFA due to a defect in peroxisomal beta oxidation

ABCD1 gene mutation leads to VLCFA accumulation in various tissues, most affected are myelin in CNS, adrenal cortex, Leydig cells = neurologic degeneration and adrenal insufficiency

R. Recognize that Addison disease (autoimmune) may occur in association with other non-endocrine disorders

50% of patients with autoimmune Addison disease have another autoimmune disease - thyroid disease is most common, followed by ovarian failure, IDDM, hypoparathyroidism, then pernicious anemia.

APS1 - mucocutaneous candidiasis, hypoparathyroidism, Addison disease, alopecia, primary gonadal failure. AIRE gene mutation. Also called APECED
APS2 - Addison disease, autoimmune thyroid disease and/or T1DM, hypogonadism, pernicious anemia, vitiligo. Also called Schmidt syndrome

S. Know that familial glucocorticoid deficiency (ACTH resistance) may be associated with achalasia and alacrima

Triple-A syndrome = alacrima, achalasia, addisonism, Also called Allgrove syndrome, caused by defects in ALADIN/AAAS gene on chromosome 12q13.

T. Understand newborn screening for congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency

Blood spot 17-OHP level is measured and compared to validated cut offs for gestational age and birthweight. High sensitivity but low PPV - any positive result must be validated with repeat 17-OHP. If abnormal, repeat 17-OHP, draw serum electrolytes, and start HC and flornief pending result.

U. Know the long-term outcome of the disorders associated with cortisol deficiency

Lifespan similar to general population, however QOL may be poorer, high incidence of depression and disability

V. Recognize the pros and cons of adrenalectomy as a treatment for CAH

Pros: decrease adrenal androgen production, and decrease likelihood of iatrogenic Cushing syndrome.
Cons: requirement for daily GC and MC replacement, stress dosing for illnesses, major abdominal surgery, can develop feedback ACTH secreting pituitary tumors
W. Know that anti-adrenal antibodies in Addison disease are often directed at the 21-hydroxylase enzyme

Autoimmune adrenocortical deficiency = second most common cause of primary adrenocorticism. 21-hydroxylase antibodies are most common, followed by adrenocortical cell antibodies. Autoimmune adrenal disease is associated with lymphocytic infiltration of the cortex = scarring and destruction of cortical cells leading to dysfunction

X. Understand the clinical presentation and treatment of the most common forms of CAH

Most common cause: 21-hydroxylase deficiency, followed 11B-HSD deficiency. See discussion above and below, table below (at end of packet).

Y. Know the likely causes of false positive newborn screening test results for CAH

Screen sample collected before 24HOL may yield false positive. Preterm infants with immature adrenal glands may have increased adrenal metabolites to include 17-OHP - will be exacerbated by stress which is common in prematurity. Cross-reactivity with other steroids may cause false positive result. False negative may be seen if maternal steroids were given antenatally

Z. Understand why hydrocortisone or prednisone cannot be used for prenatal treatment of virilizing CAH

HC and prednisone are inactivated by placental 11B-HSD and will not enter fetal circulation

AA. Understand the relative merits of low and high dose ACTH test in evaluating the HPA axis

- High dose - give 250mcg (or 15mcg/kg) ACTH(1-24) IM or IV, measure plasma cortisol at baseline, 30, and 60 minutes.
  - Normal response = peak plasma cortisol >18 mcg/dL at 30min, > 20mcg/dL at 60min.
  - Useful to differentiate between primary and secondary AI
  - May miss mild adrenal insufficiency with large dose ACTH
  - Used to evaluate for enzyme deficiency in CAH
- Low dose - give 1mcg ACTH(1-24) IM or IV, measure plasma cortisol at baseline, 30 and 60 minutes
  - More sensitive than 250mcg test (fewer false negatives)
  - Prone to technical error in medication administration - must dilute 250mcg vial in 250mL saline, and give 1mL

BB. Understand the primary clinical and biochemical features for the various genetic defects in the cortisol biosynthetic pathway causing CAH.

See table below, brief description:

21-hydroxylase deficiency: cannot convert Progesterone to DOC, or 17-OHP to 11-deoxycortisol. Will see high Progesterone and 17-OHP, high androgens, low 11-deoxycortisol, DOC, cortisol and aldosterone, excess androgens = virilization and ambiguity for females.
11B-hydroxylase deficiency: cannot convert 11-deoxycortisol to cortisol. Will see increase in 11-deoxycortisol, increase in DOC, increase in 17-OHP, low cortisol. Suppressed renin and hypertension, salt wasting is rare. Excess androgens = virilization and ambiguity for females.

17α-hydroxylase deficiency: cannot convert pregnenolone to 17-OH preg, progesterone to 17-OHP, or produce DHEA or androstenedione. Failure of production of androgens and cortisol, with accumulation of DOC and corticosterone which have mineralocorticoid effects. Hypokalemic hypertension, elevated progesterone, pregnenolone, DOC, corticosterone. 46XY DSD with undervirilized male due to failure of production of androgens.

CC. Understand the advantages and disadvantages of prenatal treatment of CAH

Advantages: potentially prevent virilization of female fetus
Disadvantages: maternal side effects (GC excess), treatment of male and unaffected female fetuses prior to disease confirmation with unknown risk for long term effects

DD. Know that long-standing elevation of ACTH can result in the formation of adrenal rest tissue

Adrenal tissue can be found in up to 15% of normal males in rete testes due to close shared embryologic origin. Uncontrolled CAH results in stimulation of growth of adrenal rest tissue in testes = TART = testicular adrenal rest tumors. Benign, however can contribute to infertility.
<table>
<thead>
<tr>
<th>Deficiency</th>
<th>21-Hydroxylase</th>
<th>11β-Hydroxylase</th>
<th>17α-Hydroxylase</th>
<th>3β-HSD Type 2</th>
<th>P450 Oxidoreductase</th>
<th>Lipoid Adrenal Hyperplasia</th>
<th>P450 Side-Chain Cleavage</th>
<th>Aldosterone Synthase</th>
<th>Apparent Cortisone Reductase</th>
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<td>Primary affected organ</td>
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<td>Adrenal, gonads, liver, all CYP type 2-expressing tissues</td>
<td>Adrenal, gonads</td>
<td>Adrenal, gonads</td>
<td>Adrenal, gonads</td>
<td>Liver, adrenal, all H6PDH/HSD11B1-expressing tissues</td>
<td>Normal, but reduced tissue levels due to increased cortisol clearance</td>
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<tr>
<td>Glucocorticoids</td>
<td>Classic: Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced to normal, impaired stress response</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
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<tr>
<td>Mineralocorticoids</td>
<td>Classic: Reduced in SW</td>
<td>Increased, mainly precursors</td>
<td>Reduced</td>
<td>Reduced often</td>
<td>Reduced to increased</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
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<tr>
<td>Sex hormones</td>
<td>Increased</td>
<td>Increased</td>
<td>Reduced</td>
<td>Reduced in males, increased in females</td>
<td>Reduced in males, increased in females</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
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<tr>
<td>Increased marker metabolites in plasma</td>
<td>DOC, S</td>
<td>Pregnenolone, progesterone, DOC, S</td>
<td>Pregnenolone, progesterone, 17-OH-pregnenolone, DHEA</td>
<td>Pregnenolone, progesterone, 17-OH-pregnenolone</td>
<td>DOC, B, 18-OHB</td>
<td>DOC, B, 18-OHB</td>
<td>DOC, B, 18-OHB</td>
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<td>Increased marker metabolites in urine</td>
<td>THDOC, THS</td>
<td>THDOC, THB, pregnenediol, pregnanediol</td>
<td>THDOC, THS, pregnanediol, pregnanetriol</td>
<td>THDOC, THS, pregnanediol, pregnanetriol</td>
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<td>PRA</td>
<td>Classic: Increased</td>
<td>Reduced</td>
<td>Increased</td>
<td>Increased</td>
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<td>Hypertension</td>
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<td>Plasma sodium</td>
<td>Classic: Reduced in SW</td>
<td>Increased</td>
<td>Increased</td>
<td>Reduced in SW</td>
<td>Normal</td>
<td>Reduced</td>
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<td>Plasma potassium</td>
<td>Classic: Increased in SW</td>
<td>Reduced</td>
<td>Increased in SW</td>
<td>Normal</td>
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<td>Increased</td>
<td>Normal</td>
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<td>Urinary salt loss</td>
<td>Classic: Increased in SW</td>
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<td>Yes</td>
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<td>Skeletal malformation</td>
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<td>No</td>
<td>Yes i</td>
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