John Sutton, DO, FACOI, FACE, CCD

Carson Tahoe
Endocrinology
Carson City, NV
KCOM Class of 1989
Gonadal Physiology and Disease
Gonadal Axis

- Hypothalamic-pituitary-gonadal
- Feedback mechanisms important
- Without production of hormone end products, axis should respond
No Disclosures
Hypergonadotrophic Hypogonadism

- Elevated gonadotropins (LH/FSH)
- Low gonadal hormones
Hypogonadotrophic Hypogonadism

- Low or inappropriately normal gonadotropins
- Low gonadal hormones
24 Year Old Male

- Female body habitus
- Lack of secondary sex characteristics
- Absent facial hair
- Infertility
- Physical exam: small testicles, Tanner I
Laboratory

- Elevated LH, FSH, Low testosterone total, free and bioavailable
- Normal prolactin
- Normal thyroid function
- Pituitary is responding appropriately to an end organ hormonal deficiency
Diagnosis

Hyper-gonadotrophic Hypogonadism
Additional Testing

- Karyotype: check for Klinefelter syndrome
  47 XXY
# Hypergonadotrophic Hypogonadism

- Germ cell arrest
- Surgery, chemotherapy
- Mumps
- Alcohol
- Immune
- Intra-abdominal testicles
14 Year Old Male

- Lack of secondary sex characteristics
- Gynecomastia
Laboratory

- Low LH, FSH
- Low total and low bioavailable (active) testosterone
- Normal prolactin
- Normal thyroid function
Diagnosis

Hypogonadotrophic Hypogonadism
Differential Diagnosis

- Delayed puberty
- Kallman syndrome: anosmia, deficiency in GnRH
- Hyperprolactinemia
- Hemochromatosis or infiltrative
- Hypopituitarism
- Neoplasm (Brain or pituitary)
- Anorexia, excess exercise
Treatment

- If fertility is in question, will require HCG or GnRH administration
- For restoring male hormone levels without fertility: testosterone IM, transdermal patch or gel, including axillary administration
- Exogenous Testosterone suppress axis
Hyperprolactinemia

- Hypothyroidism
- Pituitary neoplasm
- Non-fasting
- Medications

TREATMENT: Medical
44 Year Old Male

- Breast tenderness, decreased sex drive
- Breast enlargement, normal genital exam
Laboratory

- Normal estradiol, low free and total testosterone
- Normal B-HCG
- Normal gonadotropins
- High prolactin
- Normal thyroid function
Diagnosis

Hypogonadotrophic Hypogonadism due to Hyperprolactinemia
Treatment

- Evaluate MRI for pituitary/brain lesion
- Treatment of pituitary lesion: medical with Carbergoline or Bromocriptine
- Rare to require surgery
- Visual field testing if large tumor & compressing optic chiasm
Differential Diagnosis

- Gynecomastia common in elderly, obese, puberty
- High estradiol may represent a testicular or adrenal neoplasm
- High HCG suggests testicular or pulmonary neoplasm
- Hypothyroidism
Differential Diagnosis

- **Hypothyroidism**: promotes increased prolactin, suppression of gonadotropins, low male hormone, infertility, gynecomastia
16 Year Old Female

- Lack of secondary sex characteristics
- No menses, primary amenorrhea
Laboratory

- Low LH, FSH
- Low estradiol
Diagnosis

Hypogonadotrophic Hypogonadism
Hypogonadotrophic Hypogonadism

- Pituitary tumors
- Kallman syndrome (anosmia)
- Anorexia Nervosa
- Excessive exercise
Additional Findings with similar history but elevated LH & FSH

- Short stature
- Prepubertal genital exam
- These patients have primary amenorrhea with no history of menses
- Secondary amenorrhea refers to absent menses after menarche
Diagnosis

Hypergonadotrophic Hypogonadism
Turner Syndrome
Hypergonadotropin Hypogonadism

- Menopause ovarian failure
- Surgical removal of ovaries
- Turner Syndrome 45 X0
Secondary Amenorrhea

- Polycystic ovarian syndrome: adequate estrogen, excess androgen
- Uterine defects and trauma
- Pregnancy, profound stress
- Systemic illness
Hirsutism

- Check DHEAS and Total testosterone: Neoplasm considered with DHEAS twice normal (adrenal) and Testosterone total > 200 ng/dl (ovarian) or as low as 150 ng/dl

- Consider congenital adrenal hyperplasia, Cushing Syndrome, virilizing tumors, PCO
Disease of the Adrenals
Zona Glomerulosa

- Mineralocorticoids: aldosterone
- Angiotensin II/renin regulation by sympathetic tone; High potassium will stimulate and ACTH
- Increase in aldosterone leads to salt and water retention
- Increase in Angiotensin II leads to vasoconstriction
Zona Fasiculata and Reticularis

- Glucocorticoids: Cortisol
- Androgen: DHEAS
- Regulated by ACTH
Steroid Production Pathway (steroidogenesis)

- Baseline substrate = cholesterol
- Precursors: DHEAS
  - 17-OH progesterone
- End products: estradiol, cortisol, aldosterone
20 year old female

- Weight loss, easy tanning, nausea, vomiting, abdominal pain, weakness, dizzy

- BP=70/30, tan, confusion
Laboratory

- Hyponatremia
- Hyperkalemia
- Low glucose
- Elevated BUN/Cr
- Vitiligo
- Deficiency of all steroids
Diagnosis

Primary Adrenal Insufficiency
LABORATORY

- AM cortisol, ACTH
- Cortrosyn (ACTH) stimulation IV or IM Baseline, 30 min and 60 minute values for cortisol
- If Aldosterone drawn with Cortrosyn stimulation, response blunted

**Cortisol Goal > 18 micrograms/dl with Cortrosyn Stimulation, assuming a normal baseline cortisol**
Etiology

- 80% Autoimmune/Idiopathic
- 20% Tuberculosis
- Other: Vascular, infectious, AIDS, trauma, mets, meds, congenital adrenal hyperplasia
Autoimmune Etiology

- Addison Disease
- May be associated with other autoimmune conditions, as in Hashimoto or vitiligo
50 year old female

- Similar symptoms to index patient: low to low normal BP, fatigue weakness
- No change in skin color
- COPD
Laboratory

- Low sodium
- Normal potassium—{Suggests normal aldosterone production}
- Low ACTH or inappropriately normal when the end organ value is low
Additional History

- History of long term steroid use IV and oral treatment
- Recent change in pharmacy
- Prednisone not renewed
- Presents with fever and lung infiltrate
Secondary Adrenal Insufficiency
Etiology

- Steroid dependent
- Tumor, infection, radiation, surgery, trauma involving hypothalamic region or pituitary
Physical findings in AI

- Generalized abdominal tenderness
- Fever
- Postural hypotension
- Look for precipitating infection
- Careful with consideration for surgical abdomen
- Surgery could precipitate adrenal crisis if adequate steroids are not on board
Adrenal Insufficiency

- Electrolyte imbalance: Hyponatremia, Hyperkalemia in primary adrenal insufficiency
- Hypotension and medical crisis
- Hyponatremia without hyperkalemia in secondary adrenal insufficiency, less likely to result in adrenal/medical crisis
Electrolyte imbalance in AI

- 85 to 90% of patients have hyponatremia
- Mineralocorticoid deficiency results in sodium loss and volume depletion and increased Vasopressin secretion due to loss of cortisol
- Hyperkalemia in 60 to 65% of patients
- Rare hypercalcemia
Consider CT of the adrenals for primary adrenal insufficiency

MRI of the brain for secondary adrenal insufficiency unless the cause is evident

CT Adrenals: primary----small adrenal glands
Treatment at diagnosis in Crisis

- IV hydrocortisone 100 mg q 6-8 hrs wean as tolerated to daily oral dose of 25 mg daily/divided
- Saline and glucose
- Supportive and correcting precipitating factors
- Primary adrenal insufficiency: Florinef as aldosterone replacement
- If steroids < 30 days in general medical treatment, do not necessarily need to wean
Crisis Intervention

- Surgery
- Acute illness
- Additional steroids IV and/or PO
- Home illness: short course of double dose steroids
- Observe sodium, potassium and BP; Pt can follow BP at home for crisis intervention
25 Year Old Female

- Weight gain, hirsutism, diabetes, osteoporosis

- Centripetal obesity, striae, acne, hypertension, capillary fragility, amenorrhea
Diagnosis

Cushing Syndrome
Laboratory

- 1 mg overnight dexamethasone suppression testing; 1 mg Dex 11 pm with 8 am cortisol next day---may identify subtle with normal urine free cortisol---goal suppression < 3 to 5 some endocrinologists say less than 2
- 24 hour urine free cortisol at least a few times normal result
- Hypokalemia, hyperglycemia
- Some false positives
Pregnancy Striae
Differential Diagnosis

- Cushing disease: Cushing syndrome due to pituitary adenoma/high ACTH-dependent
- ACTH Independent vs ACTH Dependent
- Exogenous steroids
- Adrenal adenoma or hyperplasia
- Ectopic: lung tumor
Differential Diagnosis

- Cushing disease and ectopic have higher ACTH.

- Adrenal disease is ACTH independent.

- Clarification required with additional dexamethasone testing including urinary testing.
Imaging

- Cushing disease: MRI of the pituitary
- Cushing syndrome: CT or MRI of (adenoma vs hyperplasia) adrenals
- Ectopic: localize source
Treatment

- Pituitary: surgery, radiation, anti-adrenal drugs
- Ectopic: surgery, drugs
- Adrenal: surgery, drugs
Adrenal Carcinoma

- Metastatic at diagnosis
- Presents with weight loss
- Rapid onset
- Typical excessive activity of steroidogenesis pathway, not typical insufficiency
35 Year Old female

- Hypertension
- Hypokalemia
- Thin
- Metabolic alkalosis
Diagnosis

Hyperaldosteronism
Hyperaldosteronism

- Biochemical work-up first
- Low renin/high aldosterone is primary
- High renin/high aldosterone is secondary
- Elevated 24 hour urine aldosterone on high sodium diet and off diuretics
- Saline Suppression Testing
Hyperaldosteronism

- Adrenal adenoma (Conn Syndrome) “APA”
- Aldosterone Producing Adenoma
- Idiopathic Hyperaldosteronism “IHA” with bilateral disease
Secondary Hyperaldosteronism

- Sodium restriction
- Renal disease
- High Potassium intake
- Pregnancy
- Diuretics
Localization testing

- Cat Scan
- Nuclear imaging with Iodocholesterol
- Adrenal venous sampling—Gold Standard
# Adrenal Venous Sampling Summary

**RE:** Male  
**DOB:** 1942

<table>
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<tr>
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<th>Aldosterone (ng/dL)</th>
<th>Cortisol (ug/dL)</th>
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<td><strong>Basal:</strong></td>
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<tr>
<td>Right adrenal vein</td>
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<tr>
<td>Peripheral Arm</td>
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<td><strong>POST ACTH:</strong></td>
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<td>Peripheral Femoral Vein</td>
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Treatment

- Aldosterone producing adenoma: surgery; takes 6 months for final htn results, may have underlying essential HTN but hypokalemia should resolve; Spironolactone in patients with poor surgical risk

- Bilateral adrenal disease: restrict sodium, spironolactone use, no surgery
40 Year Old Male

- Hypertension unresponsive to meds
- Normal electrolytes
- Thin
- Headache, palpitations
Diagnosis

Pheochromocytoma
Laboratory

- Check 24 hour urine fractionated catecholamines, fractionated metanephrines, VMA
- 24 hour urine testing off meds if possible
- Some endocrinologists recommend serum catecholamine/metanephrine testing
Imaging

MRI or CT: MRI may help with difference in signal intensity T1/T2—bright signal in pheo

MIBG (Metalogobenzylguanidine) nuclear imaging tracer concentrates in catecholamine producing cells
Treatment

- Alpha blockers preferred
- Avoid Beta Blockers, which can precipitate a pheo crisis without alpha blockade on board
- Avoid adrenal biopsy of a lesion that is not yet evaluated for pheochromocytoma
Incidental Adrenal Adenoma

- Benign adenomas common
- Avoid imaging until biochemical diagnosis
- Evaluation important with coexisting HTN, hypokalemia, hirsutism
Adrenal Incidentaloma

Lesions discovered “inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to the suspicion of adrenal disease”
Prevalence

- In autopsy series 2.1 %
- More identified with better imaging
- Prevalence of 4.3 % in patients with a previous diagnosis of cancer
- Higher with aging at 7 % in 70 +
- More lesions in women—related to who is being tested
Causes

- Pathology: Cancer patients \( \frac{3}{4} \) mets, No history of cancer \( \frac{2}{3} \) benign
- 70% non-functioning in patients without endocrine symptoms
- 5-10%-----Cushing Syndrome, subclinical
Natural History of lesion size

- 25% of lesions larger than 6 cm represent adrenal cancer
- Up to 25% of adrenal lesions may grow 1 cm, but the significance of size change is not known
- Adrenal Cancer rapid growth “doubling time”
Natural History of function

- Up to 20% may develop a functional component.
- Development of function more common in larger neoplasms (3 cm)---this evidence can depend on study follow-up length and methods.
- Less than 3 cm neoplasms rarely change in function.
Adrenal Incidentaloma Diagnosis

- Function
- Surgical resection vs non-surgical treatment
- Malignant vs benign