Emerging Challenges in Primary Care: 2017

Primary Care Endocrinology: The Adrenal and Pituitary Herding Horses and Zebras
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Disclosures

- **Robert S. Busch, MD, FACE** serves as a speaker for Astra Zeneca, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, and Shire. Dr. Busch also serves as a researcher for Astra Zeneca, Novo Nordisk, Janssen, and Amgen.

- **Mark Stolar, MD** serves as a speaker and advisory board member for Astra Zeneca
Learning Objectives

- Differentiate adrenal gland disorders and classify them as either hyperfunctioning or hypofunctioning based on the provided clinical and laboratory information

- Recognize the preferred treatment option(s) for specific adrenal gland disorders

- Learn when clinical symptoms are indicative of functional disorders rather than disease

- Become familiar with ongoing pituitary disorders in primary care patients
Lets start up top:
Getting to know the pituitary
Normal Pituitary Hormone Secretion

Prolactinoma
Definition

- Pituitary tumors (also called adenomas) which secrete excessive amounts of prolactin
- Represent most common type of pituitary tumor seen clinically
- May exist “silently” in 5-10% of the adult population
- Micro- vs. macroadenoma (10 mm)
Regulation of pituitary hormones

- Thyroid, cortisol, growth hormone and sex hormones are under stimulatory control.

- Prolactin is under inhibitory control by dopamine from hypothalamus. Therefore anything that presses on pituitary stalk will raise prolactin.

- When TSH climbs in primary hypothyroidism, prolactin secretion is stimulated.

- ADH (antidiuretic hormone) is secreted in hypothalamus and stored in posterior pituitary. Nocturia/polyuria can be a sign of significant pituitary pathology.
Hyperprolactinemia
Definition

- Prolactin level > 30 ng/mL
- Prolactin is the hormone that stimulates milk production by the breasts
- Normal prolactin level: 15-25 ng/mL
- Several causes
  - Levels > 200 ng/mL are almost always associated with a prolactin-secreting tumor
Hyperprolactinemia
CAUSES

- Modest prolactin elevation (30 - 100 ng/ml)
  - Pregnancy (early)/Lactation
  - Stress (discomfort, exercise, low blood sugar)
  - Hypothyroidism
  - Kidney failure
  - Liver failure
  - Medications
  - “Stalk Effect"
  - Other
Drug-Induced Hyperprolactinemia

- Typically associated with prolactin levels less than 100 ng/mL (rarely > 150 ng/mL)

- Dopamine Antagonists
  - Phenothiazines
  - TCA’s
  - Metoclopramide

- SSRIs

- Estrogen/Progesterone

- Methyldopa

- Verapamil

- GnRH analogs (leuprolide, goserelin, naferelin)
Hyperprolactinemia
PRESENTATION

- **WOMEN** (manifestations of estrogen deficiency)
  - Irregular menstrual periods or amenorrhea
  - Infertility
  - Galactorrhea
  - Reduction in sex drive
  - Vision loss/Headache possible (microadenoma)
  - Osteoporosis (long-term)
Hyperprolactinemia
PRESENTATION

- **MEN**
  - Manifestation of loss of sex hormone (testosterone) production
    - Loss of libido
    - Erectile dysfunction
    - Loss of body hair
  - Vision loss/Headache more likely (macroadenoma)
  - Osteoporosis (long-term)
Hyperprolactinemia

DIAGNOSIS

- Signs or Symptoms (sex hormone deficiency)
- Elevated Prolactin level (> 30 ng/mL)
- Perform a complete pituitary hormone evaluation (especially if macroadenoma)
- Imaging Studies (MRI, CT) of the pituitary gland

IMPORTANT RULE: Prolactinomas keep same characteristics. Microadenomas rarely grow into macroadenomas. Serial MR not needed for followup
Prolactinomas
TREATMENT

- **Drug Therapy**
  - Bromocriptine (Parlodel)
  - Cabergoline (Dostinex)

  Both drugs are D2 receptor agonists; stimulate postsynaptic dopamine receptors in the hypothalamus to release dopamine; bind to D2 receptors on cell membrane of prolactin-secreting cells, inhibiting release and synthesis of prolactin.

- **Surgery**
  - Transsphenoidal surgery

- **Radiotherapy**
  - Stereotactic radiation (Gamma Knife)
  - External beam radiation
Hyperprolactinemia
TREATMENT

- Drug Therapy
  - Bromocriptine
    - Generic
    - 2.5 mg and 5 mg tabs/caps
    - Higher incidence of nausea; preferred for fertility
    - Initiate at 1.25 mg QD-BID (with meal); increase weekly
    - Maximum dose 15 mg per day
  - Cabergoline
    - Often effective in patients whose prolactinomas are resistant to bromocriptine therapy
    - Better GI tolerance
    - 0.5 mg tablets
    - Initiate at 0.25 mg twice a week
    - Max dose of 1 mg twice weekly
Hyperprolactinemia
TREATMENT

- Drug Therapy Effects
  - Normalization of serum prolactin levels
  - Restoration of gonadotropin production
  - Decrease tumor size

- Monitoring
  - Resolution of symptoms
  - Prolactin levels: repeat after 3-4 weeks
  - Tumor size: repeat MRI in 6-12 months
Hyperprolactinemia

TREATMENT

- Drug Therapy
  - Adverse Effects
    - Bromocriptine
    - Cabergoline
      - Nausea, diarrhea
      - Headache
      - Orthostatic hypotension, dizziness
      - Heart valve disorders
  - Contraindications
    - Nursing moms, uncontrolled HTN, orthostasis, heart valve d/o’s
  - Drug Interactions
    - Dopamine antagonists, 3A4 metabolism
Prolactinoma
Definition

- Pituitary tumors (also called adenomas) which secrete excessive amounts of prolactin
- Represent most common type of pituitary tumor seen clinically
- May exist “silently” in 5-10% of the adult population
- Micro- vs. macroadenoma (10 mm)
Growth Hormone Excess
Sandy Allen
World’s Tallest Woman
Robert Waldow
“The Alton Giant”
Growth Hormone Excess

- Clinical presentation
  - Children (Giantism) vs. Adults (Acromegaly)
  - Enlarged hands and feet (new ring/shoe size)
  - Excessive sweating
  - Coarse facial features
  - Multiple skin tags
  - Deepened voice
  - Osteoarthritis
  - Carpal tunnel syndrome
  - Sleep apnea
  - Headache/Visual disturbances
  - Increased risk of DM, colonic polyps, colon cancer, and coronary artery disease
Abbreviations Used Throughout

ACC – adrenal cortical carcinoma

ACTH – adrenocorticotropic hormone

APA – aldosterone-producing adenoma

BAH – bilateral adrenal hyperplasia

BUN – blood urea nitrogen

CD – Cushing’s disease

CRH – corticotropin-releasing hormone

CS – Cushing’s syndrome

Dex-CRH – dexamethasone-corticotropin releasing hormone

DST – dexamethasone suppression test

EAS – ectopic ACTH secretion

GRA – glucocorticoid-remediable aldosteronism

h – hour

HPA – hypothalamic – pituitary – adrenal

HTN – hypertension

IAH – idiopathic adrenal hyperplasia

IV – intravenous

MR – mineralocorticoid receptor

PHA – primary hyperaldosteronism

TSS – transsphenoidal surgery

UAH – unilateral adrenal hyperplasia

UCF – urine free cortisol
Hypothalamus – Pituitary – Adrenal Axis

Hypothalamus

Corticotropin-Releasing Hormone (CRH)

Anterior Pituitary

Adrenocorticotropic Hormone (ACTH) [Corticotropin]

Adrenal Cortex

Androgens, Cortisol

The Big Picture

Adrenal Cortex Disorders

Hyperfunction
- Cushing’s Syndrome
- Hyperaldosteronism

Hypofunction
- Addison’s Disease
- Congenital Adrenal Hyperplasia
- Hypoaldosteronism
Cushing’s Syndrome
(Hyperfunction of the Adrenal Gland)

- **Etiology**
  - Excess levels of glucocorticoids from endogenous production or exogenous sources

- **Classification**
  - ACTH-dependent (80%)
    - Cushing’s disease (85%)
      - A specific type of CS caused by a pituitary adenoma
    - ACTH-independent (20%)
      - Adrenal adenomas
      - Adrenal carcinomas

### Clinical Features and Overlapping Conditions of Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Features Discriminating CS</th>
<th>Common and/or Less Discriminatory CS Features</th>
<th>Overlapping Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Facial plethora (i.e. redness in the face)</td>
<td>- Acne</td>
<td>- Hypertension</td>
</tr>
<tr>
<td>- Proximal myopathy or muscle weakness</td>
<td>- Back pain</td>
<td>- Hypokalemia</td>
</tr>
<tr>
<td>- Striae, especially if reddish-purple and &gt; 1 cm wide (i.e. stretch marks)</td>
<td>- Changes in appetite</td>
<td>- Incidental adrenal mass</td>
</tr>
<tr>
<td>- Unexplained bruising or osteoporosis</td>
<td>- Decreased concentration and libido</td>
<td>- Kidney stones</td>
</tr>
<tr>
<td>- Weight gain and decreased growth velocity (children)</td>
<td>- Depression</td>
<td>- Polycystic ovary syndrome</td>
</tr>
<tr>
<td></td>
<td>- Dorsocervical fat pad (i.e. buffalo hump)</td>
<td>- Type 2 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>- Fatigue</td>
<td>- Unusual infections</td>
</tr>
<tr>
<td></td>
<td>- Facial fullness</td>
<td>- Vertebral osteoporosis</td>
</tr>
<tr>
<td></td>
<td>- Hirsutism or female balding</td>
<td></td>
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<td></td>
<td>- Impaired memory</td>
<td></td>
</tr>
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<td></td>
<td>- Insomnia</td>
<td></td>
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<tr>
<td></td>
<td>- Irritability</td>
<td></td>
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<tr>
<td></td>
<td>- Menstrual abnormalities</td>
<td></td>
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<tr>
<td></td>
<td>- Obesity</td>
<td></td>
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<td></td>
<td>- Peripheral edema</td>
<td></td>
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<tr>
<td></td>
<td>- Supraclavicular fullness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Thin skin or poor skin healing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Weight gain</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CS – Cushing’s syndrome

Cushing’s Syndrome Presentation
(Hyperfunction of the Adrenal Gland)

A) Central obesity

B) Facial rounding
“Moon Face,”
facial plethora,
supraventricular
fat pads

C) Dorsocervical fat pad
“Buffalo Hump”

Cushing’s Syndrome Presentation
(Hyperfunction of the Adrenal Gland)

D) Reddish-purple striae
“Stretch Marks”

Images: https://www-upToDate-com.elibrary.amc.edu/contents/epidemiology-and-clinical-manifestations-of-cushings-syndrome?source=search_result&search=moon+face&selectedTitle=1~150#
Diagnosis of Cushing’s Syndrome
(Hyperfunction of the Adrenal Gland)

- Involves two parts
  - Identifying the presence of hypercortisolism
  - Determining the etiology
- Most patients with Cushing's symptoms DO NOT have Cushing's
- However because Cushing's can be intermittent a negative workup isn’t always negative

Diagnosis of Cushing’s Syndrome
(Hyperfunction of the Adrenal Gland)

- Involves two parts
  - Identifying the presence hypercortisolism
    - 24-hour urine free cortisol (UFC)
      - Empty bladder first thing, upon awakening
      - Collect all subsequent voids, including the next day’s first morning void
      - Refrigerate collection, but do not freeze
      - Values over 100 suspicious
    - Late-night salivary cortisol
      - Collected between 2300 and 2400
      - Values over 3 suspicious
    - Overnight, low-dose dexamethasone suppression test (DST) or 48-hour, 2 mg DST
      - Low Dose DST: 1 mg is taken orally between 2300 and 2400
      - Longer low-dose DST: 0.5 mg taken orally every 6 hours for 48 hours
      - Fasting plasma cortisol is obtained between 0800 and 0900
      - Values over 2.0 suspicious
Cushing’s Syndrome Suspected

Exclude Exogenous Glucocorticoid Use

Perform 1 of the Following

- 24-h UFC (≥ 2 tests)
- Overnight 1-mg DST or, in select patients, the 48-h, 2 mg DST
- Late-Night Salivary Cortisol (≥ 2 tests)

Any Abnormal Result

Exclude Physiologic Causes

- Perform 1 or 2 different tests from above. May consider repeating abnormal test, Dex-CRH or midnight serum cortisol, in select patients

Any Normal Result

Cushing’s Syndrome Unlikely

Discrepant

Additional Evaluation

Abnormal

Cushing’s Syndrome
<table>
<thead>
<tr>
<th>Test</th>
<th>Benefits</th>
<th>Confounders</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-Night Salivary Cortisol</td>
<td>- Accurate</td>
<td>- Chewing tobacco</td>
<td>- Suggestive of CS if salivary cortisol is &gt; 145 ng/dL</td>
</tr>
<tr>
<td></td>
<td>- Convenient</td>
<td>- Circadian rhythm can be lost in patients with depressive illness, the</td>
<td>- Late-night nadir lost in CS</td>
</tr>
<tr>
<td></td>
<td>- Highly correlated with serum free cortisol</td>
<td>critically ill and shift workers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Reproducible</td>
<td>- Licorice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Stable for 1 week</td>
<td>- Smoking</td>
<td></td>
</tr>
<tr>
<td>Serum Cortisol After Low-Dose DST</td>
<td>- Preferred in patients with renal failure</td>
<td>- Alcohol</td>
<td>- Suggestive of CS if serum cortisol is &gt; 1.8 mcg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Estrogen</td>
<td>- Longer low-dose DST improves specificity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medications that induce or inhibit CYP3A4 metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Urine free cortisol</td>
<td>- Good choice during pregnancy and cyclic CS</td>
<td>- Acute stress</td>
<td>- Concentrations greater than the upper limit of normal for an assay are</td>
</tr>
<tr>
<td></td>
<td>- Measures only unbound cortisol, ∴ unaffected by</td>
<td>- Alcoholism</td>
<td>suggestive of CS</td>
</tr>
<tr>
<td></td>
<td>CBG-altering conditions or medications</td>
<td>- CI&lt;sub&gt;Cr&lt;/sub&gt; &lt; 60 mL/min</td>
<td>- Ensure an adequate collection by measuring urine creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Greater than 5 L of H&lt;sub&gt;2&lt;/sub&gt;O per day increases UFC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medications (carbamazepine, fenofibrate, topical steroids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Starvation</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBG – corticosteroid-binding globulin; CI<sub>Cr</sub> – creatinine clearance; CS – Cushing’s syndrome; DST – dexamethasone suppression test; H<sub>2</sub>O – water; ULN – upper limit of normal; ∴ - therefore
Diagnosis of Cushing’s Syndrome
(Hyperfunction of the Adrenal Gland)

Involves two parts - Determining the etiology:

- Adrenal vein catheterization
- Cavernous sinus sampling
- **Chest or abdominal computed tomography (CT)**
- Corticotropin-releasing hormone (CRH) stimulation test
- Desmopressin stimulation test
- Hexarelin stimulation test
- High-dose dexamethasone suppression test
- **Inferior petrosal sinus sampling (IPSS)**
  - Most sensitive test for Cushing’s syndrome
- Insulin-induced hypoglycemia
- **Jugular venous sampling (JVS)**
- Loperamide test
- Metyrapone stimulation test
- Naloxone CRH
- **Pituitary magnetic imaging resonance (MRI)**
- **Radioimmunoassay (RIA) / Immunoradiometric assay (IRMA)**
  - Used to assess plasma ACTH concentrations
- Radionuclide imaging
- Somatostatin receptor scintigraphy

ACTH-Dependent or -Independent Cushing’s Syndrome (Hyperfunction of the Adrenal Gland)

Hypothalamus → Anterior Pituitary
- Corticotropin-Releasing Hormone (CRH)
  - Adrenocorticotropic Hormone (ACTH) [Corticotropin]
  - Cortisol

Differential Diagnosis
(Hyperfunction of the Adrenal Gland)

- Iatrogenic (exogenous) Cushing’s syndrome
  - Most common cause
  - Medications to consider
    - Glucocorticoids
    - Medroxyprogesterone acetate
    - Megestrol acetate
- Pseudo-Cushing’s syndrome

Treatment of Cushing’s Syndrome
(Hyperfunction of the Adrenal Gland)

- Goals
  - Normalize cortisol levels or action at its receptors to eliminate signs and symptoms of Cushing’s syndrome
  - Prevent or treat comorbidities resulting from hypercortisolism
    - e.g., cardiovascular, diabetes mellitus, mood/cognition, infections, osteoporosis, quality of life

- Treatment of choice
  - Surgical resection by an *experienced surgeon*

General Monitoring

- Assess for clinical response
- Assess for eucortisolism, except for mifepristone
  - 24-hour urine free cortisol
  - Morning serum cortisol
  - Serum cortisol day curves
- Assess for adrenal insufficiency
  - Severe fatigue, muscle weakness, weight loss, hypotension, nausea, vomiting

Hyperaldosteronism\textsuperscript{1,20}  
(Hyperfunction of the Adrenal Gland)

- Primary hyperaldosteronism
  - Etiology
    - Bilateral adrenal hyperplasia (BAH) [65%]
    - Aldosterone-producing adenoma (APA) [30%]
  - Clinical presentation
    - Arterial hypertension, resistant to medications
    - Hypokalemia in severe cases
    - Muscle weakness
    - Some patients may be asymptomatic

- Secondary hyperaldosteronism
Primary Hyperaldosteronism\(^1,\!^20\) 
(\textit{Hyperfunction of the Adrenal Gland})

- **Who should be screened?**
  - Moderate or severe HTN
  - HTN resistant to pharmacotherapy
    - Systolic blood pressure $> 140$ mm Hg or diastolic blood pressure $> 90$ mm Hg despite $\geq 3$ antihypertensives
  - Hypertensive patients with spontaneous or diuretic-induced hypokalemia
  - HTN with an adrenal incidentaloma

- **Detection**
  - Plasma-aldosterone-concentration-to-plasma-renin-activity (PAC-to-PRA) ratio
    - PAC-to-PRA of 30 OR
    - PAC-to-PRA of 20 with aldosterone $> 15$ ng/dL
    - 24 hr urine aldosterone above 14 on high salt diet
Primary Hyperaldosteronism\textsuperscript{1,20} (Hyperfunction of the Adrenal Gland)

- Confirmatory testing (no gold standard)
  - Captopril challenge test, fludrocortisone suppression test, oral sodium loading, saline infusion

- Subtype classification, as the management is different
  - Unilateral (i.e. APA or UAH) – the treatment of choice is laparoscopic adrenalectomy
  - Bilateral (i.e. bilateral APA, IAH) - the treatment of choice is a mineralocorticoid receptor (MR) antagonist
  - GRA – the treatment of choice is a long acting glucocorticoid (e.g., dexamethasone, prednisone)
# Primary Hyperaldosteronism
(Hyperfunction of the Adrenal Gland)

## Therapeutic Options for the Management of Bilateral Adrenal Disease

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Pros</th>
<th>Cons</th>
<th>Comments and Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>- Oral agent (take with food)</td>
<td>- Less effective than spironolactone</td>
<td>- Blood pressure</td>
</tr>
<tr>
<td></td>
<td>- Well tolerated</td>
<td>- Caution with renal impairment</td>
<td>- Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <em>Adverse effects</em>: GI, hyperkalemia [BW]</td>
<td>- Serum creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Titrate every 4 to 8 weeks</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>- Less sex steroid-dependent effects</td>
<td>- CYP3A4 substrate</td>
<td>- Blood pressure</td>
</tr>
<tr>
<td></td>
<td>- Selective aldosterone antagonist</td>
<td>- Caution with renal impairment</td>
<td>- Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 60% MR antagonist potency of spironolactone</td>
<td>- Serum creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <em>Adverse effects</em>: hyperkalemia, hypotension</td>
<td>- Titrate every 4 to 8 weeks</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>- Lots of data</td>
<td>- Nonselective aldosterone antagonist with active metabolites</td>
<td>- Consider a thiazide diuretic, amiloride or triamterine to</td>
</tr>
<tr>
<td></td>
<td>- <strong>Preferred MR antagonist</strong></td>
<td>- <em>Adverse effects</em> (dose dependent): GI, gynecomastia, hyperkalemia,</td>
<td>avoid higher spironolactone doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>impotence, menstrual irregularities</td>
<td>- Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>- Serum creatinine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Titrate every 4 to 8 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: BW – boxed warning; GI – gastrointestinal; MR – mineralocorticoid receptor
The Big Picture

Adrenal Cortex Disorders

**Hyperfunction**
- Cushing’s Syndrome
- Hyperaldosteronism

**Hypofunction**
- Addison’s Disease
- Congenital Adrenal Hyperplasia
- Hypoaldosteronism
Addison’s Disease
(Hypofunction of the Adrenal Gland)

- **Primary adrenal insufficiency**

- **Etiologies**
  - Developed vs. underdeveloped countries
  - Consider autoimmune polyendocrine syndrome (APS)
  - Medication-induced
    - Phenobarbital, phenytoin, rifampin, steroidogenesis inhibitors


Secondary Adrenal Insufficiency
(Hypofunction of the Adrenal Gland)

- Etiology
  - Many!
  - Exogenous steroid use
    - Decreases ACTH \(\rightarrow\) decreased glucocorticoids
  - Medications to consider
    - Glucocorticoids
    - Medroxyprogesterone acetate
    - Megestrol acetate

Adrenal Fatigue: Not a Real Entity

- Basal cortisol daily secretion is 30mg. Under stress it can climb to 300mg (ten-fold reserve)

- Adrenal function is reduced in the setting of untreated hypothyroidism hence the internet link to Hashimoto’s

- Every adrenal fatigue book lists weight gain as a symptom. Weight loss is a cardinal symptom of adrenal insufficiency

- Unnecessary steroid replacement carries long term risk, even with “natural” adrenal extracts
Diagnosis

- Addison’s disease
  - Abnormal corticotropin stimulation test response
    - Cosyntropin (Cortrosyn) – synthetic ACTH
  - Dehydration, hyponatremia, hyperkalemia, increased BUN and weight loss
  - Hyperpigmentation

- Secondary adrenal insufficiency
  - Preserved aldosterone secretion

Hyperpigmentation in Addison’s Disease
(Hypofunction of the Adrenal Gland)
Goals

- Use the lowest effective dose to mimic the diurnal adrenal rhythm

Treatment of choice: exogenous steroids

- Preferred agents (total daily dose)
  - Cortisone acetate (25 to 37.5 mg daily)
  - Hydrocortisone (15 to 25 mg daily)
  - Prednisone (2.5 mg daily)

- Administered twice daily with the majority (67%) given in the morning then dose two, six to eight hours after the morning dose
  - e.g., Hydrocortisone 20 mg by mouth in the morning then 10 mg six to eight hours later
# Relative Potencies of Glucocorticoids

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Antiinflammatory Potency</th>
<th>Equivalent Potency (mg)</th>
<th>Approximate Half-Life (minutes)</th>
<th>Sodium-Retaining Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>25</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>20</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3.5</td>
<td>5</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>5</td>
<td>200</td>
<td>1</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>4</td>
<td>300</td>
<td>0</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>4</td>
<td>180</td>
<td>0</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0.6</td>
<td>100 to 300</td>
<td>0</td>
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<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0.75</td>
<td>100 to 300</td>
<td>0</td>
</tr>
</tbody>
</table>


Supplemental Glucocorticoid Use¹
(Hypofunction of the Adrenal Gland)

- Very important to educate patients about
  - Strenuous activities (e.g., exercise)
    - Additional 5 to 10 mg of hydrocortisone before activity
  - Illness and injury
    - At minimum, double the daily dose until recovery
    - Parenteral therapy will be necessary if patients experience diarrhea or vomiting
      - e.g., glucocorticoid suppositories or injectable hydrocortisone
Treatment of Addison’s Disease
(Hypofunction of the Adrenal Gland)

- Fludrocortisone acetate
  - “Synthetic aldosterone”
  - Not always required
    - Some glucocorticoids have sodium-retaining abilities
      - e.g., cortisone, hydrocortisone, prednisone, prednisolone
    - Usually 0.05 to 0.2 mg once daily will suffice
- Monitoring
  - Blood pressure and electrolytes (e.g., Na\(^+\), K\(^+\))

Principles of Glucocorticoid Therapy

- Oral agents are well absorbed

- Adverse effects
  - Cataracts
  - HPA axis suppression
  - Hypokalemia
  - Hypomagnesemia
  - Iatrogenic Cushing’s syndrome
  - Increased risk for infections
  - Osteoporosis
  - Peptic ulcer disease
  - Seizures
  - Sodium retention → edema
HPA Axis Suppression

- Increased risk with higher doses and longer durations of therapy
  - Assess for HPA axis recovery
    - Morning cortisol every 3 months until ≥ 7.4 mcg/dL
    - Then ACTH stimulation test
    - If either baseline or ACTH stimulation test cortisol levels are ≥ 18 mcg/dL the axis has recovered

- Alternate-day therapy
  - Consideration for *stable patients* on long-term therapy

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Acute Adrenal Insufficiency
(Hypofunction of the Adrenal Gland)

- Also known as an Addisonian crisis
- An emergency
- Most common etiology
  - Use of exogenous steroids chronically followed by abrupt withdrawal
- Management
  - Hydrocortisone 100 mg IV bolus then 10 mg/h continuous infusion or intermittent boluses of 100 to 200 mg daily
    - Switch to oral therapy when stable
    - Usually after 24 to 48 h
  - Fluid replacement will be needed

### Factors of Successful Glucocorticoid Therapy

<table>
<thead>
<tr>
<th>Counseling</th>
<th>Monitoring</th>
<th>Recognizing Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider the use of a medical alert bracelet</td>
<td>Bone mineral density scans</td>
<td>Delayed and insidious: atherosclerosis, cataracts</td>
</tr>
<tr>
<td>During times of stress you will need to increase your dose</td>
<td>Growth and development (children and adolescents)</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Never stop taking the medication without first talking with your provider</td>
<td>Ophthalmologic exams</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Take with food to decrease stomach upset</td>
<td>Serum electrolytes</td>
<td>Likely to occur early in therapy and usually</td>
</tr>
<tr>
<td></td>
<td>Serum glucose</td>
<td>unavoidable: increased appetite, insomnia, weight</td>
</tr>
<tr>
<td></td>
<td>Stool tests for occult blood loss</td>
<td>gain</td>
</tr>
</tbody>
</table>

**Abbreviations:** HPA – hypothalamic-pituitary-adrenal


Pheochromocytoma: When is anxiety more than anxiety??

- Only 2000 cases per year diagnosed in USA
- Rule of tens: 10% in children 10% bilateral 10% non-adrenal 10% malignant
- Most common symptoms are headaches, sweats and palpitations
- Hypertension the rule but orthostatic hypotension can be seen in epinephrine secreting tumors
- Weight loss is a clue. Weight gain is NOT seen in pheo
Diagnosis of Pheochromocytoma

- Since pheo is rare workup is designed to exclude not diagnose

- Plasma metanephrines most specific if over 4 fold elevated. If 2-4 fold elevated doing 24 hr urine catecholamines/metanephrines worthwhile

- If slightly elevated just repeat. 30mins supine usually not needed

- Chromogranin-A if elevated makes neuroendocrine cause more likely but is falsely elevated if taking a PPI
Conclusions

- Adrenal disorders can be classified as either hyperfunctioning or hypofunctioning
- Most patients with adrenal symptomatology don’t have adrenal pathology
- Iatrogenic Cushing’s syndrome is the most common cause of Cushing’s syndrome
- Patients must be educated about the appropriate use of glucocorticoids
  - Not stopping long-term therapy abruptly
  - Increasing supplemental doses, as needed
Endocrinology in Primary Care: Take Home Points

- Most patients with symptoms don’t have an endocrine cause. Horses are more common than zebras. Look for symptoms that just don’t fit before going too far.

- Prolactin secreting microadenomas typically remain benign and stable and often needn’t be treated especially post menopausal.

- Adrenal disorders are relatively uncommon. Obesity, fatigue and anxiety are VERY common. Accurate screening tests to exclude disease help clinicians and patients focus on the real issues at hand.