Demystifying Medicine: Addison’s Disease Meets Chromatin Biology

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Disclosure

- Adrenal Section editor and author, UpToDate
Cortisol is a bi-modal hormone

- Made by the adrenal gland cortex (outer layer)
- Baseline/day-to-day control of metabolism (fuel)
- Stress → increased amounts immunosuppressant and anti-inflammatory
Adrenal Gland Hormones

Cortisol (glucocorticoids)
Aldosterone (mineralocorticoids)
DHEA (androgens)
Hypothalamic-Pituitary-Adrenal Axis
Cortisol daily rhythm
The right amount of cortisol is critical

- Too much
- Just right!
- Too little

Cushing’s Syndrome
Adrenal Insufficiency
Untreated, complete adrenal insufficiency leads to circulatory collapse and death.
FAQs about Adrenal Insufficiency

- Causes
- Diagnosis
  - Clinical Features
- Adrenal fatigue
- Steroid Replacement
The HPA Axis in Adrenal Insufficiency

Normal Adrenal Insufficiency
- CRH from hypothalamus
- ACTH from pituitary
- Cortisol from adrenal

Primary Adrenal Insufficiency
- CRH from hypothalamus
- ACTH from pituitary
- Cortisol from adrenal

Secondary Adrenal Insufficiency
- CRH from hypothalamus
- ACTH from pituitary
- Cortisol from adrenal

Renin and ALDO are also involved in the feedback loop.
### Primary Adrenal Insufficiency: Causes

<table>
<thead>
<tr>
<th>Causes</th>
<th>Suggestive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary AI</td>
<td>Pigmentation, hypotension</td>
</tr>
<tr>
<td>Idiopathic Autoimmune</td>
<td>Most common</td>
</tr>
<tr>
<td>Infections: TB, fungal, AIDS-associated (CMV)</td>
<td>15% of patients in US series</td>
</tr>
<tr>
<td>Space occupying mass</td>
<td>Metastases (lung, breast, kidney, gut, lymphoma), blood, heparin Rx</td>
</tr>
<tr>
<td>Bilat Adx or Rx</td>
<td>Ketoconazole, mitotane, aminoglutethimide, metyrapone, etomidate</td>
</tr>
<tr>
<td>Polyglandular Failure 1</td>
<td>Hypopara, candidiasis, vitiligo; &lt; 20y</td>
</tr>
<tr>
<td>Polyglandular Failure 2</td>
<td>IDDM, hypothyroid, alopecia areata, hypogonadal; &gt;40 yo</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>X-linked; cognitive, gait, paraparesis</td>
</tr>
</tbody>
</table>
## Secondary Adrenal Insufficiency: Causes

<table>
<thead>
<tr>
<th>Causes</th>
<th>Suggestive Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression of the HPA axis by endogenous/exogenous GCs</td>
<td>Rx history; Cushing’s history</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Usually ICU admission; also sports-related</td>
</tr>
<tr>
<td>Structural lesions of the hypothalamus or pituitary: tumors, destruction by infiltrating disorders, x-ray, lymphocytic hypophysitis.</td>
<td>Other pituitary deficiencies</td>
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<tr>
<td>Isolated ACTH deficiency</td>
<td></td>
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<tr>
<td>FAQs about Adrenal Insufficiency</td>
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<tr>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>• Causes</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis</td>
<td></td>
</tr>
<tr>
<td>– Clinical Features – <strong>recognition</strong></td>
<td></td>
</tr>
<tr>
<td>• Adrenal fatigue</td>
<td></td>
</tr>
<tr>
<td>• Steroid Replacement</td>
<td></td>
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</tbody>
</table>
Adrenal insufficiency is suggested by clinical features and confirmed by biochemical testing.
Clinical Acumen in Adrenal Insufficiency: Classic presentation

- Classic symptoms: fatigue, malaise, anorexia, weight loss, abdominal pain, vomiting
- Hyponatremia +/- hyperkalemia
- Presentation related to rate of onset and severity of deficiency
- Primary adrenal failure – both glucocorticoid and mineralocorticoid deficiency
- Secondary adrenal failure – may have manifestation of other hormone deficiencies
Primary Adrenal Insufficiency

• **Acute:** orthostatic hypotension, circulatory collapse, fever, and hypoglycemia

• **Chronic:** fatigue, anorexia, weight loss, joint and back pain, and darkening of the skin

• Since all layers of the adrenal cortex are involved, both mineralocorticoid and glucocorticoid secretion is impaired. Thus, laboratory findings include hyponatremia and hyperkalemia.
Recognition (pre-test probability) depends on perspective
The Rheumatologist’s perspective

- Knee pain
- Knee flexion
- Failure of knee extension
- Back pain
- Migratory arthralgias
- Myalgias

The psychiatrist’s perspective

- Psychosis
- Anxiety, depression
- Lethargy, weariness “too tired to vomit”
- “Most of our [untreated] patients are hypoglycaemic in the early morning, being difficult to rouse from sleep, and their attitude towards those who make the attempt being surly and resentful.
- I do not suggest, of course, that such behaviour is confined to Addisonian patients.”

The Dermatologist’s perspective: Primary AI

- Increased pigmentation of mucosa, creases, scars, nipple
- Generalized hyperpigmentation
- Vitiligo
- Nail bed lines
Skin features of primary adrenal insufficiency: Bronzing

Photos courtesy of DL Loriaux
Hyperpigmentation
Skin features of primary adrenal insufficiency: Hyperpigmentation
Skin features of primary adrenal insufficiency: Hyperpigmentation
Hyperpigmentation?
Skin features of primary autoimmune adrenal insufficiency: Bronzing & vitiligo
Addison’s diagram of vitiligo and hyperpigmentation

Thomas Addison, *On the constitutional and local effects of disease of the supra-renal capsules.*
Refresher course for general practitioners (1950): Addison’s Disease

- “Hiccup, yawning, conjunctivitis, grimaces, involuntary cries, negativism, contrariness and apathy.
- Sensitivity to cold, with curling up under the bedclothes, and subnormal temperature.
- A man age 36 was operated on for a perforated duodenal ulcer…” Nothing was found. At necropsy, TB of adrenals
- Normal pregnancy, vomiting, malaise, in a dark skinned woman

Simpson SL. BMJ 4689: 1164, 1950
Neurology and Psychiatry

• Collapse and syncope “sinking spells”
• Hiccough
• Pain (back, abdomen, chest, thighs, epigastrium, head, knees, plantar feet)
• Pseudoperitonitis (7%)
• Irritability, insomnia, restlessness, poor concentration
• Suspiciousness, agitation, delusions, hallucinations, bizarre posturing, confusion

Confusing clinical presentations

- Pregnancy: Early symptoms easily confused with hyperemesis gravidarum
- HIV/CMV: Fatigue mis-interpreted
- ICU: Etomidate effects overlooked
- Drugs (injection, skin whitening): Cushing’s syndrome may be suspected
- Celiac disease: GI symptoms overlap
FAQs about Adrenal Insufficiency

• Causes
• Diagnosis
  – Clinical Features
• Adrenal fatigue
• Steroid Replacement
Adrenal Fatigue
Adrenal fatigue

• A collection of nonspecific symptoms, such as body aches, fatigue, nervousness, sleep disturbances and digestive problems.

• A mild form of adrenal insufficiency caused by chronic stress so that the adrenal glands are unable to keep pace with the demands of perpetual fight-or-flight arousal.

• Usually “diagnosed” via questionnaire or salivary cortisol samples

• Conventional tests for adrenal insufficiency not done
Questions to diagnose adrenal fatigue

• You may be experiencing adrenal fatigue if you regularly notice one or more of the following:*
• You feel tired for no reason.
• You have trouble getting up in the morning, even when you go to bed at a reasonable hour.
• You are feeling rundown or overwhelmed.
• You have difficulty bouncing back from stress or illness.
• You crave salty and sweet snacks.
• You feel more awake, alert and energetic after 6PM than you do all day.

http://www.adrenalfatigue.org
Causes of adrenal fatigue

Factors Affecting The Adrenals

- Financial pressure
- Negative attitudes & beliefs
- Lack of relaxation
- Psychological stress
- Unwanted unemployment
- Fear
- Trauma
- Caffeine
- Nutritional deficiency
- Marital stress
- To little or too much exercise
- Wound healing
- Death of a loved one
- Repeated stresses
- Toxins
- Infection: Acute & Chronic
- Emotional stress
- Allergies
- Over exertion
- Smoking
- Lack of sleep
- Poor eating habits
- Drugs & white flour
Treatment of adrenal fatigue

• Supplements for “adrenal gland support” + 2-5 g Vit C; Ca, Mg, licorice root extract; Vit E
• Diet (regular meals; chew well; slow carb; no junk food; 5-6 veggies/d; sea salt; Vit E with mixed tocopherols; B-complex
• Lying down during work breaks (preferably at 10 a.m. and again anytime 3 - 5 p.m.)
• Sleeping until 9 a.m. often
• Laughing; do something fun each day
• Exercising
• Minimizing stress
• Taking negative people out of your life
Endocrine society/ the Hormone Health Network ‘fact sheet”

http://www.hormone.org
FAQs about Adrenal Insufficiency

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• Diagnosis
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Treatment of adrenal insufficiency

- **Acute:** Saline, hydrocortisone (dexamethasone)
- **Chronic:**
  - **Glucocorticoid:** Hydrocortisone (10 - 12 mg/M2) OR prednisone (4 - 7.5 mg) OR dexamethasone (250 - 500 ug)
  - **Mineralocorticoid:** Florinef (50 - 400 mg)/ liberal salt
  - Consider dose adjustment and metabolism issues
  - **Androgen:** DHEA not proven except for puberty
What is the goal of glucocorticoid replacement?

Mimic normal physiology
amount of cortisol production
pattern of production

Mah et al. Clin Endo 2004
What’s Best?
Once, twice, or thrice?

Actually, it is not well studied. Patients differ in their preference.
The RR and 95% CI for all-cause mortality in patients with Addison's disease in Sweden from 1987-2001

<table>
<thead>
<tr>
<th>Obs. no.</th>
<th>Exp. no.</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>507</td>
<td>199</td>
</tr>
<tr>
<td>men</td>
<td>208</td>
<td>95</td>
</tr>
<tr>
<td>women</td>
<td>299</td>
<td>104</td>
</tr>
</tbody>
</table>

Bergthorsdottir, R. et al. J Clin Endocrinol Metab 2006;91:4849-4853
Other “treatment”

- MedicAlert or similar jewelry
- Injection and stress doses teaching
- Education
Thank you!
Hydrocortisone

• Split dose for most people (2 – 3 x daily)
• Take first dose on wakening, or earlier with alarm
• Take second dose in afternoon – patient can determine time
• For severe evening tiredness, a small dose
• Maintain total daily dose within the split
• New formulations are coming
Medication adjustments

- Clinical signs of excess (Cushingoid, osteoporosis)/deficiency (salt craving, fainting, fatigue, weight loss)
- Primary
  - Renin levels, potassium
  - Adjust mineralocorticoid first
  - ACTH levels remain elevated
- Measure bone mineral density
- Quality of life measurements?
- Sick day rules
Plasma ACTH levels after ACTH-(1–24) and insulin

- Mean peak ACTH after insulin: 69.6 ± 9.3 pmol/L (range, 33.6–126.0 pmol/L).
- This level was lower than after 1.0-µg ACTH: 120.2 ± 15.5 pmol/L.
- The duration of the increase in plasma ACTH during the insulin hypoglycemia test was about 7-fold greater than after 1.0-µg ACTH.

Nye EJ et al. J Clin Endocrinol Metab 84:3648, 1999
Adrenal Support
Dose-dependent effects of ACTH

- Compared to the HDT, the cortisol responses in the LDTs were shorter, with all levels declining at 60 min.
- Peak cortisol levels in all LDTs were significantly lower than those in the HDT.
- The cortisol level and range at 30 min were similar in the 1.0-µg LDT and the HDT.

Nye EJ et al. J Clin Endocrinol Metab 84:3648, 1999
The Adrenal Axis

CRH  \[\rightarrow\] ACTH  \[\rightarrow\] Cortisol  \[\rightarrow\] CRH

Glomerulosa  \[\downarrow\]  Fasciulata  \[\downarrow\]  Reticularis  \[\downarrow\]  Medulla

http://www.udel.edu
Adrenal Insufficiency Physiology

CRH → ACTH → Cortisol → ALDO → Renin → CRH

CRH → ACTH → Cortisol → ALDO → Renin → CRH

http://www.udel.edu
The Adrenal Axis

CRH

ACTH

Cortisol

Glomerulosa

Fasciulata

Reticularis

Medulla

http://www.udel.edu
For more information

- Consult Dr. Wilson's book, *Adrenal Fatigue: The 21st Century Stress Syndrome*. It contains a wealth of insights and a series of tests you can do at home, as well as lab tests like the saliva test for adrenal hormones to help you determine if you are experiencing adrenal fatigue.*

  Also see [Could I be experiencing adrenal fatigue?](http://www.adrenalfatigue.org)

- [http://www.adrenalfatigue.org](http://www.adrenalfatigue.org)