Chronic Stress and the Adrenal Gland
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February 2013

Objectives
- Functional Medicine approach to Adrenal exhaustion/fatigue
- Definition and Stages of Adrenal Exhaustion
- Testing to suggest adrenal origin to exhaustion
- Treatment approach to help your patients
- Testing to rule out pathology/other etiology (brief)

Why Bother talking about this?
- Enough to learn
- Most Doctors don’t know about it
- Why Bother?
  - Common: you are seeing it most days in clinic and probably not yet able to help these people.
  - Extremely practical: You can use yourself or a family member as a learning lab.
  - Commonly known in all other health care systems (allopathic medicine is the outlier)

Cases
- 46 y/o Latina woman with fatigue requiring her to nap after work and not able to play with her kids, normal labs, works cleaning houses, states all is fine and no stress.
- 28 y/o woman with can’t work as she is too tired. Brain Fog all afternoon and evening. Making mistakes at work.
- 31 y/o resident was given supplements by a friend and noticed that when he is taking them his head is above water and when he is not he is buried.

Stress: acute vs. chronic
- Hans Selye: Adaptation to Stress (1930’s)
- Hormones: over 50 secreted by adrenals
- Acute: flight or fight (freeze, seek comfort)
- Chronic: emotional fragility, physical vulnerability, decreased ability to recover
- Severe: Addisons

Adrenal Glands
- 2 small glands on top of kidney
- 50 hormones (epi/adrenaline, cortisol, progesterone, testosterone, DHEA, estrogen…)

Thanks to Wendy Kohatsu, Filomena Trindade, James Wilson, Alan MacDaniels
The Adrenal Cortex

The adrenal cortex is composed of 3 distinct layers:

- 1. zona glomerulosa
  - the outermost layer comprising approximately 5% of the cortex
  - its main hormone is **aldosterone**

- 2. zona fasciculata
  - the middle layer comprising approximately 70% of the cortex
  - its main hormone is **cortisol**

- 3. zona reticularis
  - the inner layer of the cortex comprising approximately 25% of the cortex
  - its main hormones are the sex hormones of adrenal origin: **DHEAS**, **DHEA**, **androstenedione**, **estrogen**, **progesterone** and **testosterone**

The Adrenal Gland: Normal function

**Cortisol** is the top priority hormone.

- Every human cell has a cortisol receptor.
- The adrenal gland makes a lot of cortisol
  - one of the few truly essential hormones.
  - 100 to 1,000 times more than aldosterone
- Available to physicians in the early ’50s.
- First for patients dying of Addison’s disease
  - promptly, miraculously restored.
- Oral replacement dose for Addison’s disease is 25–30 mg cortisol daily.

The Adrenal Gland: Dysfunction

Addison’s disease: Fatal if untreated.

Symptoms of Addison’s: The top four
- chronic, worsening fatigue;
- loss of appetite
- muscle weakness;
- weight loss.

Other symptoms include:
- irritability and depression
- hypoglycemia,
- irregular menstrual cycles
- craving salty foods
- nausea,
- vomiting
- diarrhea
- polyuria

Addison’s disease: Fatal if untreated.


High Cortisol: Cushing’s

*Signs and Sx of Prolonged Stress*

- James Wilson’s book *Adrenal Fatigue*
  - Classic stress history
  - Fatigue (late: not relieved by sleep)
  - Mid afternoon crash
  - Salt cravings and Sugar cravings
  - Frequent illnesses or Prolonged recovery
  - Lower BP S<120 often <110
  - Pupil response: does not stay contracted
  - Other

*Signs*

- BP: low (S <120 and/or mildly orthostatic)
- Skin: decreased blood flow → waxy manila
- Pupil: can’t sustain contraction to light
Maladaptive adrenal stress responses

**Chronic Stress:**

After weeks of severe situational stress, pituitary gonadotropin production is inhibited:
- Women stop menstruating and
- Men’s testosterone drops.
- PTSD patients have the same low cortisol as over-trained marathon runners (over-trained athlete syndrome).

**The Adrenal Gland Dysfunction**

PTSD features symptoms and abnormalities characteristic of low adrenal steroid production
- As does the Over-trained Athlete Syndrome.
- As does Chronic Fatigue Syndrome.

The common denominator is “stress”

The adrenal is the stress gland.
- Ya think there’s a connection?


Adrenal “Fatigue”

- Stuck in vast gray zone between
  - Addison’s disease (adrenal depletion)
  - Cushing’s Syndrome (adrenal excess)
- **When is “normal”, not normal?**
  - Postulate there is spectrum of manifestations
- Adaptation to chronic stress (Hans Selye)
  - Phases: Alarm → Resistance → Exhaustion
  - Sx: Decreased ability to deal with stress, cortisol depletion, early aging
  - Affects adrenal cortex

Pathophysiology

- What we are taught: Pathology
- What we are teaching: “pre-pathology” approximately like DM and insulin resistance or IGT

Stages of Adrenal Dysfunction

- Stage I: alarm=normal adaptation
  - Both Cortisol and DHEA increase
  - May be ASx
- Stage II: resistant phase/early decompensation
  - Cortisol increased and DHEA decreased
  - “stressed”, anxiety attacks, mood swings
- Stage III: exhaustion phase/late decompensation
  - Low Cortisol and low DHEA
  - Depression and Exhaustion
  - Fatigue not relieved by sleep

High Adrenaline

- Losing weight
- Anxious
- Severe hot flashes (if perimenopausal)
- Cold (compensatory hypothyroid/rT3)
- Muscle wasting unless actively building
High Cortisol
- Depressed +/- anxiety
- Weight around midsection
- Frequent infections
- Elevated Cholesterol
- Any of the high adrenaline symptoms

Harmful Effects of High Cortisol
- Decreased antibody and Ig production
- Decreased number and function of WBC’s
- Fluid retention and Hypertension
- Higher blood glucose/Insulin Resistance
- Redistribution of fat from thighs and buttocks to waist and neck

Stress and Fat-Metabolic Syndrome
- Stress induces Cortisol
- Cortisol stimulates gluconeogenesis
- Glucose is released into Blood Sugar
- Insulin resistance increases
- Insulin resistance leads to higher blood glucose
- HUNGER!

Abdominal fat deposition
- Cortisol and insulin contribute to redistribution of fat
Testing to confirm thoughts

- Testing Here (all serum)
  - Cortisol am
  - DHEA
  - +/- ACTH
- Testing Boutique
  - 4 point salivary cortisol
  - Urine Metabolites ($220)
  - +/- ACTH (serum)

Normal vs Optimal

- Shoe size
- Cortisol
- DHEA

The non-boutique testing

- Snap shot measure
  - Serum DHEA (see normals table below)
  - First am serum Cortisol (see normals table below)

- Limitations and better tests available
  - Classic symptoms and r/o negative (CBC, CMP, TSH, Ferritin) very helpful.
  - We also follow therapy by sx and follow up tests.

DHEA

<table>
<thead>
<tr>
<th>Approx'n's</th>
<th>20 y/o (DHEA falls approx 2%/yr)</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1800-1250</td>
<td>Approx 700-800</td>
<td>Approx 600-700</td>
<td>Approx 500-600</td>
</tr>
<tr>
<td>Women</td>
<td>800-980</td>
<td>500-600</td>
<td>400-500</td>
<td>300-480</td>
</tr>
</tbody>
</table>

Plasma Free Cortisol – Range

- 8:00 AM 2-25 mg/dl (optimal 15-22)
  - Very low <5 (extremely low ? Addisons <3)
  - Low <10
  - Moderately low 10-15
  - Good 15-22
  - High >22
- 4:00 PM 3-16 mg/dl (optimal 10-14)

- 4 years of age: same ref range as adult.
  Typical lab reference ranges are excessively broad and therefore, do not detect most cases.
  Suspect low adrenal function if symptoms are present and results are lower than optimal levels.
Recall from WK: Differential Diagnosis

- Psychologic
  - Depression
  - Anxiety
  - Somatization d/o
  - Drug addiction/wd
  - Seasonal affective d/o
- Pharma
  - Hypnotics
  - Antihypertensives
  - Antidepressants
  - Antihistamines
- Endocrine
  - Hypothyroidism
  - DM

Differential Diagnosis (cont.)

- Cardiopulmonary
  - CHF
  - COPD
  - Sleep apnea
- Infectious
  - TB
  - HIV
  - Mononucleosis
  - CMV
- Musculoskeletal
  - Rheumatic dx
  - Chronic pain (inadequately treated)
  - Dental disease
  - “Idiopathic”
  - Chronic fatigue
  - CFS
  - Fibromyalgia

Workup of patient with fatigue

- History, history, history
  - Including occupation, meds, OTCs, stressors
- Don’t forget ROS
  - Gyn – menorrhagia, Endo- cold/hot intolerance
  - Pulm – snoring.
- Basic labs
  - CBC, CMP (glucose, lytes, LFTs), TSH
  - Ferritin
  - Vitamin D, 25-OH

Other systems

- Lack of Jing (vital force-Qui, Chi, Prana)
- Vata Imbalance
- Adrenal Fatigue

BMJ. 2003;326(7399):1124.
**Treatment General**

- **Stage I: relaxation > repletion**
  - Turn off faucet
- **Stage II: relaxation = repletion**
  - Turn off faucet and mop up floor
- **Stage III: repletion > relaxation**
  - (long term) sometimes 2-3 years.
  - Really help them rebuild

**Treatment: two ways to approach**

- **Stage I: stress management, sleep, vata pacification, vit B and C, ORS, Imagnesium**
- **Stage II: as above, DHEA men, and Pregnenolone women, possibly add herbs**
- **Stage III: as above add adrenal glandulars, note: cortisol only in selected patients tailor to this patient: review Treatment pyramid to help**

**IM4Us Treatment Pyramid**

- **Environment**
- **Relationship**
- **Resources**
  - Patient-Centered Goals
  - Internal Environment
  - Lifestyle
  - Natural Therapies
  - Conventional Medicine

**Adrenal Rx Simple (all phases)**

- **Proper nutrition**
  - No caffeine, low carb, high quality carbs,
  - Eat regular meals
- **Supplements:**
  - Vitamin C – 1000mg 2x a day
  - B-complex/B 50 – thiamine, B3, B5, B6, B12 2x a day
  - Magnesium – 500 -1000 mg, start 250 2x/d
  - Omega 3 fish oils — 1-3 gm

*Clin Clim Acta 1975; 65:251*

*Altern Med Review 2009; 14(2):114-140 **excellent review*

*Nutrition 2005;21:705*

**Phase I**

- **Something for relaxation**
  - Yoga, Tai Chi, Breathing, etc
  - Chamomile Tea
  - L-Theanine 150mg up to 3 times a day (theanine serine-source naturals)
- **Regularity:** meals, routine, sleep wake
- **Sleep:** minimum of 8 hours a night
- +/- supplements (generally will vit C,B,Mg, omega 3’s)
- Prevent it from getting worse

**Theanine**

- Influences the secretion and function:
  - Dopamine
  - Serotonin
- Exerts anti-stress effects during an acute stress challenge
- Dose dependant presence of brain alpha waves within 40 minutes of ingesting 200 mg

Altern Med Rev. 2005; 10(2): 120-130*
Phase II
Like phase I but will add:
- Pregnenolone for women
  - 10mg in the evening
- DHEA for men
  - 25mg in the morning

Phase III: Add Adrenal glandulars
- Why? Theory: give back building blocks needed for repair
- Brands:
  - Metagenics Adrenogen®
    - raw bovine adrenal concentrate + B6+pantothenic acid
  - Cytozyme AD, Biotic
- Dosing: 1-3 tabs q am, then add 1-3 tabs right as they go to sleep, then add 1 in afternoon if not feeling much better.

Some like herbs- Adaptogenic herbs

Rhodiola rosea
- Demonstrated effects in cortex and hypothalamus
- Seems to prevent depletion of adrenal catecholamines.
- Signif improvement in HAM-A, decreased stress-related fatigue, and salivary cortisol
- Physicians on night-duty
  - 50 mg bid of standardized extract – improved psychomotor fxn, mental performance and well-being

Adaptogenic herbs
- Siberian Ginseng (Eleutherococcus senticosis)
  - Most extensively used in Russia
  - Review of >2000 pts shows better tolerance to physical and mental stress, and preserved work fxn
  - Korean ginseng (Panax ginseng spp.)
    - Animal studies support effect on HPA axis
    - Limited human studies
- Licorice (Glycyrrhiza glabra)
  - Binds to glucocorticoid and mineralocorticoid receptors, weak mimick
  - Can spare cortisol by extending its half-life
  - Dose: 0.7 g/day glycyrrhizic acid

Follow up
- Getting better or not
- Trouble shoot and move to next step
- Sleep?
- Stress?
- Meals
- Movement
- Supplements
- ?more testing

Even more radical… or sane?
- Give body back cortisol (hydrocortisone)
- NOT prednisone
- 1 mg prednisone = 5 mg hydrocortisone
- Start with LOW DOSE hydrocortisone
  - 2.5 mg in am
  - 2.5 mg at noon
The adrenal cortex responds with cortisol.
- Increases available energy
  - increases blood sugar production
  - reduces conversion of amino acids to protein
  - mobilizes free fatty acids;
- Increases the metabolism, including
  - respiratory rate,  - heart rate,
  - cardiovascular tone  - blood pressure
- Sharpens brain function:
  - aroused and more vigilant
- Enhances normal immune function

The Adrenal Gland: Treatment

Criticism of cortisol therapy:
Prior studies of “low-dose” treatment for CFS gave more than physiological dose:
- We make 25–30 mg hydrocortisone daily.
- This equals 5 mg Prednisone.
- “Low-dose” studies gave Prednisone ≥ 7.5 mg
  - That is not a low dose!
Resulting adrenal suppression in 12 of 30.

Effects of slow, deep breathing
- Increases arterial baroreflex sensitivity
  Circulation. 2002 Jan 15;105(2):143-5
- Self-perceived reductions in levels of tension and anxiety
  Biofeedback Self Regul. 1990 Sep;15(3):273-84
- Increases resting oxygen saturation and improves exercise tolerance

Relaxation Practice and the Mind-Body - Heart
- 107 patients with ischemic heart disease
- 16 1.5-hour sessions of stress management
38-month risk for cardiac events 0.26 vs. conventionally treated controls (p=.04)
Blumenthal JA et al. Arch Intern Med 1997; 157:2213

Just for Comparison:
- 4S trial – RR 0.67 after 5.4 years treatment with simvastatin
  Circulation. 1998;97:1453-1460
- MIRACL Trial (higher risk patients, like the relaxation trial): RR 0.84 in 16 weeks on atorvastatin 80 mg vs. placebo
  JAMA. 2001;285:1711-1718
- LIPS – RR 0.78 after 3-4 years post PCI on fluvastatin 80 mg vs. placebo
  JAMA. Vol. 387 No. 24, June 26, 2002
- EUROPA and HOPE trials show approximately 20% reduction in risk of events over 4 to 5 years of treatment with an ACEI
  Lancet 2003 Sep 6;Vol. 362 (9386), pp. 755-7
Cases

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Cortisol: 12
- Very low <5, Low <10, Moderately low 10-15, Good 15-22, High >22

DHEA: 120

Summary Slide

- Adrenal Issues are a spectrum
  - from Cushing's to Addison's and in between
- Functional testing can be done in this setting
  - need new normal's.
- Common issue with effective treatment

Good one for SR

Memory and Chronic Stress

- Long-term exposure to high endogenous levels of cortisol is associated with memory impairments.
Cortisol THREE Key Ways this affects health
- Weight
- Brain Changes
- Energy

THREE Key Ways this affects health
- Weight: High Cortisol
- Brain Changes
- Energy

THREE Key Ways this affects health
- Weight
- Brain Changes
- Energy

Excess Cortisol & Serotonin
3. "Cortisol at the nM-microM concentration range induces a substantial increase in serotonin uptake both in vitro ... and in vivo, ... owing to promotion of synthesis of the serotonin transporter".

4. "Transcription of the gene coding for tryptophan oxygenase (TO) in rat liver is induced 10-fold by glucocorticoids"
NOTE: 5-HTP bypasses the TO enzyme and thus can raise serotonin even in the face of excess cortisol

Excess Cortisol & Serotonin
1. "Corticosterone treatment was found to induce a functional decarboxylation of somatodendritic 5-HT(1A) autoreceptors."

2. Corticosterone treatment significantly decreased the number of 5-HT1A receptor sites ...

Exercise vs. Sertraline
Observed mean depression scores before and after treatment

THREE Key Ways this affects health

- Weight
- Brain Changes
- Energy: high and low cortisol

Stress and the HPT axis:

- CRH inhibits TSH directly, and TRH secondarily.
- Glucocorticoids inhibit TSH, and T4 to T3 conversion.

The Adrenal Gland: Diagnose dysfunction

The fetus in-utero is shown to be permanently affected by maternal stress - it targets the H-P axis

Horm Behav. 2009 Feb; 55(2):292-8

“Epigenetic modification”
- our body changes the way it “reads” DNA in response to environmental stimuli.

Semin Reprod Med. 2009 Sep; 27(5):358-68
Yehuda R. J Trauma Stress. 2009 Oct 7. [Epub]