Adrenal Insufficiency

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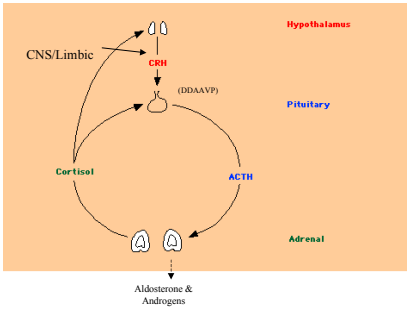
Objectives

- Epidemiology & EBM
- Anatomy & Physiology
- Etiology
- Clinical
- Labs and Imaging
- Diagnosis & DDx
- Treatment & Monitoring
- Summary
- Case

Anatomy & Physiology

- 2 glands located above kidneys
- 3 zones "Zona" in Adrenal Cortex
  - Glomerulosa - Aldosterone
  - Fasciculata - Cortisol
  - Reticularis - Androgens
- only 5-10% Cortisol free, rest bound to CBG
- Glucocorticoid

Adrenal Axis



Glucocorticoid Function

- Nuclear level
  - transcription and translation
- Also more rapid effects
  - vascular, metabolic
- Function
  - cope with stresses
  - vascular tone
  - infection/immunity
  - CHO, fat, protein metabolism

Etiology

- Need 90% destruction
- Primary
  - all zones affected
- Central
  - Pituitary & Hypothalamic
  - Aldosterone axis intact since R-A-A control

Chronic Primary Adrenal Insufficiency

- 39-60/million prevalence
- mean age 46yo (17-72yo range)

- Autoimmune 75-80%
  - sporadic
  - familial
    - polyglandular type 1 and 2
    - other autoimmune, antibodies

- Adrenomyeloneuropathy
  - young male
  - X-linked recessive
  - spastic paralysis
  - disorder of long chain fatty acid metabolism
- Infection
  - TB 20%
  - Fungi - immunocompromised, systemic
  - AIDS/Opportunistic Infection - late stage

- Mets
  - rare to cause adrenal insufficiency
  - lung, breast, melanoma, lymphoma, GI
- Medications
  - megace, ketoconazole, phenytoin, phenobarb
- Infiltrative
  - amyloid, sarcoid, hemochromatosis
- Isolated Glucocorticoid deficiency
  - familial
- CAH

Acute Primary Adrenal Insufficiency

- Bilateral Hemmorage
  - coagulopathy/drugs
  - sepsis
- necrosis
- thrombosis
  - sepsis
  - Antiphospholipid syndrome

Chronic Central Adrenal Insufficiency

- Most common cause is **exogenous glucocorticoid use**
- otherwise isolated rare
- Space Occupying Lesion
  - multi-hormones
  - structural effects

- Tumor/Malignancy*
- Craniopharyngoma*
- **XRT/Surgery**
- Hypophysitis*
- Infiltrative*
  - Sarcoid, Histio X, Amyloid, Hemochromatosis
- Empty Sella
- **Glucocorticoid treatment**
- Isolated

*often DI

Acute Central Adrenal Insufficiency

- Post-partum necrosis
- hemmoragic macroadenoma
- head injury
- Surgery (transient)

Clinical

Symptom	Frequency, percent
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6–13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (systolic BP <110 mmHg)	88–94
Vitiligo	10–20
Auricular calcification	5
Laboratory abnormality	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

Clues Primary vs Central

Primary and secondary adrenal insufficiency
Tiredness, weakness, mental depression
Anorexia, weight loss
Dizziness, orthostatic hypotension
Nausea, vomiting, diarrhea
Hyponatremia, hypoglycemia, mild normocytic anemia, lymphocytosis, eosinophilia

Primary adrenal insufficiency and associated disorders
Hyperpigmentation
Hyperkalemia
Vitiligo
Autoimmune thyroid disease
Central nervous system symptoms in adrenomyeloneuropathy

Secondary adrenal insufficiency and associated disorders
Pale skin without marked anemia
Amenorrhea, decreased libido and potency
Scanty axillary and pubic hair
Small testicles
Secondary hypothyroidism
Prepubertal growth deficit, delayed puberty
Headache, visual symptoms
Diabetes insipidus

Other Clues

- Hx Cancer, TB, HIV
- Travel History
- Family History
  - Autoimmune diseases

Specific Clues

- Primary
  - Hyperpigmentation
    - pressure, friction, sun-exposed, trauma, oral mucosa
  - Salt craving
- Central (less severe, normal K, pallor)
  - other hormones
  - structural symptoms
  - DI - may be masked

Labs

- CBC & Diff
- Lytes, renal
- Calcium
- TSH & Ab
- Coags
- Pituitary hormones

Clinical Acute

The 5 H's

- **H**ypotension
  - especially inotrope resistance
- **H**yporesponsiveness
- **H**yperkalemia
- **H**yponatremia
- **H**ypoglycemia

- "acute abdomen"

Don't forget !

- If suspect Acute Adrenal Insufficiency
  - **stat**
    - Cortisol
    - ACTH
    - ACTH Stim using Dexa as Tx ASAP

Please don't forget !!

Diagnosis

Test	Rule-in	Rule-out
8-9am Cortisol		
non-stress	< 83-100nM	> 450-525nM
stress	< 135nM	> 700-830nM
ACTH Stim cortisol 0, 30, 60min	< 500nM	> 500-550nM
Insulin Tolerance Cortisol	< 550nM	> 550nM
Metyrapone	C < 230nM 11-DC < 200nM	C > 230nM 11-DC > 200nM

Limitations of ACTH Stim Test

- 1mcg more SN than 250mcg
- therefore **1mcg** if suspect Central etiology
- not useful if
  - ? Mild Central
  - recent Central etiology
- need pharmacy to make up or yourself

Insulin Tolerance Test

- Gold standard
- $$
- time-consuming
- need BG < 2.2mM
  - contraindicated if
    - Seizure
    - CVD

Primary vs Central

Test	Primary	Central
ACTH	> 10-22pM	low or n
Aldosterone	lowish	n/high
Renin Activity	high	n/high

Pituitary vs Hypothalmic

- CRH stimulation 1mcg/kg or 100mcg
  - measure cortisol & ACTH
  - hypothalmic
    - **exaggerated** and **prolonged** ACTH response

Clues for Etiology

- Adrenal antibodies
  - Autoimmune 70% SN; >> SP
    - 21-Hydroxylase Ab; > SN & SP
- VLCFA
  - Adrenomyeloneuropathy
- Cultures & Serology, HIV testing
  - Infection
- Serology
  - Antiphospholipid Syndrome

Imaging

- MRI Sella/Pituitary
  - if central cause suspected
- CT/MRI Adrenals
  - size (autoimmune, TB/fungi, infiltrative)
  - calcification (TB/fungi)
  - hemmorage
  - abcess
  - mets
- CXR (infection, mets)

FNA Biopsy

- TB, fungi, abcess
- Mets
- Infiltrative

- usually not necessary

Tx Acute Adrenal Crises

1. Establish intravenous access with a large-gauge needle.
2. Draw blood for stat serum electrolytes and glucose and routine measurement of plasma cortisol and ACTH. Do not wait for lab results.
3. Infuse 2 to 3 liters of isotonic saline or 5 percent dextrose in isotonic saline as quickly as possible. Monitor for signs of fluid overload by measuring central or peripheral venous pressure and listening for pulmonary râles. Reduce infusion rate if indicated.
4. Inject 4 mg of dexamethasone phosphate intravenously. Intravenous hydrocortisone (100 mg immediately and every 6 h thereafter) may also be used, but will interfere with measurement of plasma cortisol during the short ACTH stimulation test. Mineralocorticoids are unnecessary at this time.
5. Use supportive measures as needed.

Always give Glucocorticoid before Thyroixine!

Tx after patient stabilized

1. Continue intravenous isotonic saline at a slower rate for next 24 to 48 h.
2. Search for and treat possible infectious precipitating causes of the adrenal crisis.
3. Perform a short ACTH stimulation test to confirm the diagnosis of adrenal insufficiency, if patient does not have known adrenal insufficiency.
4. Determine the type of adrenal insufficiency and its cause if not already known.
5. Taper glucocorticoids to maintenance dosage over 1 to 3 d, if precipitating or complicating illness permits.
6. Begin mineralocorticoid replacement with fludrocortisone (0.1 mg by mouth daily) when saline infusion is stopped.

What are some of the precipitants?

- Pus
- Pain/MI
- Paralysis/CVA
- Pancreatitis
- Peri-op
- Pharmaceuticals
- Pregnancy
- Poor-compliance
- Trauma

"The P's"

Key Questions in Dx

- Is it really Adrenal Insufficiency?
- Acute or Chronic?
- Primary or Central?
- Etiology?

- If **high suspicion**, don't wait to treat but at least get:
  - stat Cortisol & ACTH
  - treat with Dexa till ACTH stim done

Chronic Tx

Glucocorticoid replacement
1. Dexamethasone 0.5 (0.25–0.75) mg or prednisone 5 (2.5–7.5) mg orally at bedtime. Supplement with hydrocortisone 5–10 mg orally in mid-afternoon if indicated.
2. Alternative therapy is with hydrocortisone 15–20 mg upon awakening and 5–10 mg in early afternoon.
3. Monitor clinical symptoms and morning plasma ACTH.

Mineralocorticoid replacement
1. Fludrocortisone 0.1 (0.05–0.2) mg orally.
2. Liberal salt intake.
3. Monitor lying and standing blood pressure and pulse, edema, serum potassium and plasma renin activity.

Androgen replacement
1. Dehydroepiandrosterone 25–50 mg orally in women.

Patient education
1. Educate patient about the disease, how to manage minor illnesses and major stresses and how to inject dexamethasone intramuscularly.

Emergency precautions
1. Obtain Medic-Alert bracelet/necklace, Emergency Medical Information Card, and prefilled syringes containing dexamethasone 4 mg in 1 mL saline.

Treatment of minor febrile illness or stress
1. Increase glucocorticoid dose 2 to 3 fold for the few days of illness. Do not change mineralocorticoid dose.
2. Contact physician if illness worsens or persists for more than 3 d.
3. No extra supplementation is needed for most uncomplicated, outpatient dental procedures under local anesthesia. General anesthesia or intravenous sedation should not be used in the office.

Emergency treatment of severe stress or trauma
1. Inject contents of prefilled dexamethasone (4 mg) syringe intramuscularly.
2. Get to physician as quickly as possible.

Some caveats of Chronic Tx

- Tx if Sx, just don't base on testing !
  - but must Tx if "stress" situation
- No treatment if
  - mild; esp central unless "stress"
- Less Steroid replacement in Central
  - Equivalent of 20mg Hydrocortisone/d
  - no Mineralocorticoid Tx
- Most physiologic regimen:
  - **Hydrocortisone** am, lunch, and supper

Sick Day/OR Management

1. For moderate illness give hydrocortisone 50 mg twice a day orally or intravenously. Taper rapidly to maintenance dose as patient recovers.

2. For severe illness give hydrocortisone 100 mg intravenously every 8 h. Taper dose to maintenance level by decreasing in half every day. Adjust dose relative to course of illness.

3. For minor procedures under local anesthesia and most radiological studies, no extra supplementation is needed.

4. For moderately stressful procedures, such as barium enema, endoscopy, or arteriography, give a single 100 mg intravenous dose of hydrocortisone just before the procedure.

5. For major surgery, give hydrocortisone 100 mg intravenously just before induction of anesthesia and continue every 8 h for first 24 h. Taper dose rapidly, decreasing by half per day, to maintenance level.

Bottom Line

- Uncommon but can be fatal if not Tx
- Primary and Central
  - Exogenous Tx, Autoimmune, Surgery, TB
- Acute and Chronic
- Non-specific Symptoms & Signs
- Dx & DDx
  - Cortisol, ACTH, ACTH Stim, ITT
- Tx
  - Glucorticoids, Mineralocorticoids
  - Supportive & Education
- Seek out precipitants

Case

48yo woman HIV CD4 600.

3mos weakness, weight loss, fatigue, salt craving.

Menses and hair normal.

No fever, cough, TB, travel, HA, visual Sx, DI Sx.

PMH HIV, no OI
No smoke/EtOH
No thyroid disease

Meds Septra
HAART

FH no Adrenal Insuff
Mom Hypothyroid

O/E Dark, 100/60 -> 80/50**,** 70-90reg
Afebrile
Thyroid n
Vitiligo
Hyperpigment
Hair n
Fundi, VF, EOM n
DTR n
rest n

Labs nMCV Anemia
Lymph|Eosinos
K 5.0, Na 130
HCO3 20, BG 3.9
Creat 100
TSH n, Ab n, Ca n

Adrenal Ab +
ACTH Stim 250mcg
Cortisol 200 max
ACTH 30

CXR neg
CT Abdo
small adrenals, no Ca
no hemmorage

Diagnosis ?