Adrenal Insufficiency

See also Adrenal Insufficiency in Pregnancy
See also Adrenal Crisis

Background

1. Definition
   - Partial or complete loss of adrenal gland function
   - Decr production of glucocorticoids and/or mineralocorticoids by adrenal glands resulting from a defect in hypothalamic-pituitary-adrenal axis
2. General info
   - Primary adrenal insufficiency
     - Failure of adrenal gland to synthesize corticosteroids (one or both types)
   - Secondary adrenal insufficiency
     - Adrenal gland function intact but inadequate ACTH stimulation of adrenal glands
   - Can be acute or chronic process
   - 90% of gland destroyed before clinical S/Sx appear

Pathophysiology

1. Pathology of dz
   - Primary
     - Damage to adrenal gland or process that blocks cortisol synthesis, often associated with lack of aldosterone as well
     - Autoimmune
       - Most common cause in developed countries
       - 68-94%
     - Schmidt's Syndrome
       - AI or positive autoantibodies, plus autoimmune thyroiditis
     - Polyglandular Autoimmune Syn I (PGA-I)
       - Onset in childhood with mucocutaneous candidiasis, hypoparathyroid & later with hypogonad, hypothyroid, vitiligo, dystrophy of teeth & nails
     - PGA-II
       - Onset as adult autoimmune adrenalitis with autoimmune thyroiditis or DM 1
       - Can have concurrent vitiligo, celiac sprue, pernicious anemia
       - Ovarian failure in 10% women <40 yo with PGA-II
     - Carpenter syndrome
       - Autoimmune adrenalitis with autoimmune thyroiditis and DM 1
     - Adrenal hemorrhage
       - Coagulopathies, pregnancy
     - Waterhouse-Friderichsen Syndrome
       - Hemorrhage into adrenal glands assoc with sepsis, most commonly meningococcemia
     - Tuberculosis <15%, most common cause in developing countries
     - Medications
       - Ketoconazole, etomidate

        - X-linked Adrenoleukodystrophy
            - AI occurs long before CNS Sx
        - AIDS associated infections:
            - Cytomegalovirus
            - C. neoformans
            - T. gondii
            - M. avium intracellulare
            - H. capsulatum
            - P. jirovecii
        - Metastatic CA:
            - Lung, breast, kidney, colon, lymphoma
        - Misc:
            - Sarcoidosis, amyloidosis
    - Secondary
        - Decreased pituitary ACTH production
        - Abrupt discontinuation of long term corticosteroids
        - Pituitary adenomas, other tumors or inflammatory process involving sella
        - Massive hemorrhage: postpartum bleed (Sheehan's syndrome)
    - Tertiary
        - Decreased hypothalamic CRH production
2. Incidence/ prevalence
    - Primary
        - Incidence: 50 per 1 million in Western populations
        - Prevalence: 110 per 1 million in UK
    - Secondary
        - In 2003, prevalence of 150-280 per million
        - Estimated 6 million people in US have undiagnosed 2° adrenal insufficiency
3. Risk factors
    - Female 1.5-3.5x > males
    - Adrenal Cortex Antibodies confers 30% increased risk of AI
4. Morbidity/ mortality
    - Mortality 2-fold higher than background
        - Usually related to malignancy, infections or cardiovascular dz
    - Fatigue, depression, anxiety
    - Acute adrenal insufficiency may be fatal if untreated
    - Death usually from cardiac arrhythmias secondary to electrolyte imbalances
5. Etiologies
    - Primary adrenal insufficiency
        - Autoimmune disorders (80%)
            - Addison's dz
            - Autoimmune polyendocrine syndromes, Type 1 and 2
        - Infection
            - Tuberculosis
            - CMV
            - HIV
            - Coccidioidomycosis
            - Histoplasmosis

        - Drugs
            - Ketoconazole
            - Metyrapone
            - Aminoglutethimide
            - Mitotane
            - Etomidate
        - Cancer
            - Metastasis to adrenal most common (lung, GI, breast, and renal)
        - Adrenoleukodystrophy
        - Coagulopathies
        - Hx of familial glucocorticoid deficiency
        - Congenital adrenal hyperplasia
        - Adrenal hemorrhage
    - Secondary adrenal insufficiency
        - Discontinuation of exogenous glucocorticoid therapy
        - Hypothalamic: pituitary dz
            - Pituitary tumor
            - Radiation therapy to pituitary gland
        - Removal of endogenous steroid-producing tumor
            - ACTH-producing lung carcinoma
    - Acute adrenal crisis
        - Precipitated in pts with underlying adrenal dz by physiological stressors
            - Infection
            - Trauma
            - Surgery
            - Dehydration
6. Conditions assoc w/adrenal insufficiency
    - Stressors (infection, trauma, surgery or dehydration) with underlying adrenal dz
    - Inadequate exogenous replacement during infection, trauma, periods of stress
    - Coagulopathies
    - Post-partum hypopituitarism (Sheehan's syndrome)
        - Hypopituitarism secondary to necrosis due to blood loss and hypovolemic shock during and after childbirth
    - Waterhouse-Friderichsen syndrome
        - Bilateral hemorrhage of adrenal glands 2° to fulminant meningococcemia

Diagnostics

1. History
    - Acute symptoms
        - Weakness
        - Abdominal pain
        - Salt craving
        - Diarrhea/ constipation
        - N/V

        - Syncope
        - Myalgias
        - Arthralgias
    - Subacute symptoms
        - Hyperpigmentation of skin
        - Weight loss
        - Orthostatic hypotension
        - Cold intolerance
        - Amenorrhea
        - Axillary hair loss
        - Depression/ anxiety
        - Fatigue
        - Hair loss
        - Anorexia
2. Physical exam
    - Acute
        - Hypovolemic shock
        - Fever
        - N/V
        - Confusion
        - Coma
        - Tachycardia
        - Abdominal pain
        - Flank pain: from adrenal hemorrhage
    - Primary
        - Hyperpigmentation of skin (not universal)
            - Mucous membranes, lips
            - Pressure areas (knuckles, skin creases)
            - Nipples, axilla, perineum
            - Palmar creases
            - Areola, scars
            - Vagina
        - Hypotension
        - Wt loss
        - Dehydration
        - Vitiligo (9%)
    - Secondary
        - No hyperpigmentation of skin
        - Hypotension less common
        - Visual field defect (pituitary origin)
        - Headache (pituitary origin)
3. Dx testing
    - Lab eval
        - Primary
            - Hyponatremia (85-90%)
            - Hyperkalemia (60-65%)
            - Hypoglycemia
            - Normocytic normochromic anemia
            - Neutropenia

- Eosinophilia
- Lymphocytosis
- Incr BUN and creatinine 2° to dehydration

▪ Secondary
- Same as primary except potassium, creatinine, bicarbonate and BUN are usually normal

o Dx imaging
▪ Abd X-ray:
- Calcification of adrenal glands (tuberculosis)

▪ CT scan:
- Calcification, metastasis, adrenal enlargement or hemorrhage

▪ Head CT:
- Pituitary destruction, mass

o Other studies
▪ EKG
- Nonspecific ST-T wave changes due to electrolyte abnormalities

4. Other studies (if indicated)
o Screening test:
▪ 8 am serum cortisol (alt draw time for shift workers)
- Level >13 mcg/dL reliably rules out adrenal insufficiency
- Primary AI: <3 mcg/dL with elevated ACTH, usually >100 pg/mL
- Secondary AI: <3 mcg/dL with low or inappropriately normal ACTH
- Level $\leq$13 mcg/dL initiate dynamic testing

▪ NOTE:
- Serum cortisol less reliable than free cortisol in severe physical stress
- Use free cortisol if serum albumin <2.5 g/L

o Dynamic testing
▪ None of available tests are ideal in relation to sensitivity / specificity
▪ Choice of dynamic testing depends on clinical experience / considerations of test performance / available resources
▪ **Synthetic ACTH (Cortrosyn) stimulation** (SOR:C)
- Low dose: Cortrosyn 1 mcg IV, measure serum cortisol at 0, 30, & 60 min
  - More sensitive for Dx mild AI
  - Peak serum cortisol >18 mcg/dL normal; 13-17 mcg/dL indeterminate, requires confirmation with ITT; <13 confirms dx
  - Preferred initial dynamic test due to more physiologic dose, simplicity, better sensitivity and less expensive
- High dose: Cortrosyn 250 mcg IV or IM, measure cortisol at 0, 30, & 60 min (spec 95%; sens 97%)
  - Same cutoffs as low dose stim test
  - Can have falsely normal cortisol in mild AI due to hyperexaggerated stress dose at 250 mcg
- Peak of <15 mcg/dL is definitively abnormal

- NOTE:
    - Normal cortrosyn stimulation test does not rule out mild or recent onset secondary adrenal insufficiency
- **Insulin tolerance test (ITT)**
    - Relies on entire hypothalamic -pituitary -adrenal axis
    - Used when pretest probability for dz is high and normal cortrosyn stim test obtained
    - Insulin 0.1 U/kg (0.15 U/kg in obese) IV, measure serum cortisol at 0, 30, 45, 60, 90 min
    - Serum cortisol <18 and concomitant serum glucose <40 suggest AI
    - Contraindications: age >60, seizure disorder, CAD
    - Resource intensive; requires close supervision d/t hypoglycemia effect
        - Can test growth hormone reserve in pts with hypothalamic/pituitary dz
- **Metyrapone test**
    - Performed if rapid ACTH test is normal
    - Measures ability of HPA axis to respond to acute drop in serum cortisol levels
    - Metyrapone blocks final step of cortisol synthesis (11-beta hyroxylase)
        - Admin should cause an increase in ACTH and 11-deoxycortisol (cortisol precursor)
    - Overnight single dose-test
        - Metyrapone 30 mg/kg (max dose 3,000 mg) at midnight
            - Measure Serum 11-deoxycortisol and cortisol next morning (8 am)
            - Two or three day test
    - Cortisol should drop to <5 mcg/dL; deoxycortisol should incr to >7 mcg/dL
    - Low cost; safe for outpt use
    - Limitations: metyrapone intermittently available
- **CRH stimulation test**
    - High cost/low utility (high sensitivity; specificity 33%)
    - 1 mcg/kg CRH IV, measure serum cortisol at 0, 15, 30, 60 min
    - Cortisol level >18.5 mcg/dL normal
    - Peak of <15 mcg/dL is definitively abnormal

5. Identify level of dz
    - ACTH >100 pg/ml = primary adrenal insufficiency
    - ACTH infusion (250 mg/day over 8 hours) for 3-5 days
        - Daily urine 17-hydroxysteroid levels
        - Day 5 should record 3-5 fold incr 17OH steroid level
            - Diagnostic of secondary OR tertiary dz
            - Primary Adrenal Insuff: 17OH steroid does not decr
    - CRH Stimulation Test
        - Differentiates primary, secondary AND tertiary dz

6. Identify cause
    - Primary
        - Anti-adrenal antibodies (highly specific; limited sensitivity)
            - ACA (Adrenal cortex autoantibody) + 21-hydroxylase antibody (21OHab) = autoimmune adrenalitis
        - Adrenal CT scan: hemorrhage, metastatic, infectious
            - Tuberculosis work-up: adrenal CT scan
                - Enlarged adrenal gland w/classic calcifications; caseating granulomas
            - Non-caseating granulomas likely in cancer/sarcoidosis
        - Very long chain fatty acids if adrenoleukodystrophy suspected (males only)
            - MRI superior to CT for identification of mass
                - Cannot distinguish tumor vs. inflammatory process
    - Secondary
        - Pituitary / hypothalamic MRI: neoplasia (if no glucocorticoid exposure)

Differential Diagnosis

1. Key DDx
    - Chronic fatigue syndrome
    - Hypothyroidism
    - Congenital adrenal hyperplasia
    - Hypothyroidism
    - Pregnancy
    - Polyglandular autoimmune dz
    - Depression
    - Anorexia Nervosa
2. Extensive DDx
    - 3-Beta-hydroxysteroid dehydrogenase deficiency
    - Adrenal hypoplasia
    - Acanthosis Nigricans
    - Lentigo
    - Malignant melanoma
    - Melasma
    - Vitiligo
    - Birth trauma
    - Familial glucocorticoid deficiency
    - Pseudohypoaldosteronism
    - Adrenoleukodystrophy
    - Adrenomyeloneuropathy
    - Autoimmune polyglandular endocrinopathy syndromes
    - Infectious adrenalitis (HIV, TB)
    - Lipoid adrenal hyperplasia
    - Wolman disorder

Acute Treatment

1. IV saline (1-3 L) and dextrose, or saline alone, to correct
    - Volume
    - Electrolytes

- Possible hypoglycemia

2. Hydrocortisone sodium phosphate or sodium succinate 100 mg IV q6 hrs for 24 hrs; dexamethasone 4 mg IV bolus
   - If known adrenal insufficiency and potassium > 6 mEq/L, hydrocortisone preferred (mineralocorticoid activity)

Further Management (24 hrs)

1. If stable, decr hydrocortisone to 50 mg q6 hrs on day 2 and 10 mg on subsequent days
2. Fludrocortisone can be substituted (0.1 mg qD PO) for hydrocortisone once pt stable

Long-term Care

1. Maintenance hydrocortisone (HCT) varies
   - Typically 15-30 mg daily in adults
     - 10-20 in morning and 5-10 mg later in day
2. Fludrocortisone 0.05-0.2 mg PO in AM
   - Target: lower renin activity to upper normal range
3. Follow weight, BP and electrolytes regularly
4. Bone mineral density (BMD)
   - Measure annually for as long as glucocorticoid Tx is continued
5. Pts should wear medical alert bracelet
6. Periods of physiologic stress (severe illness or surgery)
   - Require transient dosages of HCT 3-10 times that for maintenance Tx
7. Stress dosages usually not needed in mild illness (URIs)
   - But can use 3x3 rule
     - 2-3 times usual dose x3 days
8. Provide inj HCT to pts and family member for adrenal crisis or when pt cannot tolerate PO meds
9. Complications of long-term steroid replacement therapy
   - Osteoporosis
   - Osteonecrosis
   - Skin thinning
   - Purpura
   - Cataracts
   - Glaucoma
   - Atherosclerosis
   - Gastritis, ulcers, GI bleeding
   - Fluid retention
   - Hypertension
   - Myopathy, muscle weakness
   - Growth retardation in children
   - Psychosis
   - Glucose intolerance, hyperglycemia
   - Neutrophilia
   - Susceptibility to infection

Follow-Up

1. Return to office
    - Chronic glucocorticoid therapy surveillance mainly based on clinical grounds
        - Serum ACTH levels and cortisol extremely variable
    - Use lowest possible dose, to avoid:
        - Obesity
        - Glucose intolerance
        - Osteoporosis
    - Often difficult to achieve correct dose of steroid replacement in pts
        - Physicians should look for S/Sx of over or under replacement
            - If corticosteroid dose excessive, pts experience wt gain and Cushing's features
            - If steroid dose inadequate, pts experience symptoms of adrenal insufficiency
    - Mineralocorticoid replacement: look for S/Sx of postural hypotension, measure
        - Supine and upright BP and pulse
        - Serum potassium
        - Plasma renin
            - Recommend annual renin levels
2. Refer to specialist
    - Consult endocrinology in all cases of adrenal insufficiency
3. Admit to hospital
    - Acute adrenal crisis (hypotensive shock) should be admitted to ICU for stabilization
    - Severe physical stress such as surgery, trauma, or serious illness should be admitted for IV hydrocortisone

Prognosis

1. Untreated:
    - Poor prognosis, usually death
2. Treated:
    - Normal lifespan, quality of life sometimes impaired due to fatigue, depression, anxiety
3. Retrospective observational study in Sweden noted 2-fold higher risk of death
    - Due to cardiovascular, malignant and infectious causes

Patient Education

1. http://www.cc.nih.gov/ccc/patient_education/pepubs/mngadrins.pdf
2. http://www.endocrine.niddk.nih.gov/pubs/addison/addison.htm#education

Evidence-Based Inquiry

1. What's the most practical way to rule out adrenal insufficiency?
2. What is the sensitivity and specificity of the cosyntropin (ACTH) stimulation test for adrenal insufficiency?

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