

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 meningococemia
 - 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 meningococemia

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
 - Dx imaging
 - Abd X-ray:
 - Calcification of adrenal glands (tuberculosis)
 - CT scan:
 - Calcification, metastasis, adrenal enlargement or hemorrhage
 - Head CT:
 - Pituitary destruction, mass
 - Other studies
 - EKG
 - Nonspecific ST-T wave changes due to electrolyte abnormalities
4. Other studies (if indicated)
- 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 ≤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
 - 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
- **Metirapone test**
 - Performed if rapid ACTH test is normal
 - Measures ability of HPA axis to respond to acute drop in serum cortisol levels
 - Metirapone blocks final step of cortisol synthesis (11-beta hydroxylase)
 - Admin should cause an increase in ACTH and 11-deoxycortisol (cortisol precursor)
 - Overnight single dose-test
 - Metirapone 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: metirapone 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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