Overview

- Adrenal insufficiency
  - Primary and central

- Adrenal fatigue

- Adrenal nodules
  - Incidental adrenal nodule
  - Functional adrenal nodule
    - Adrenal Cushing, Primary Hyperaldosteronism and Pheochromocytoma

Adrenal Physiology
Adrenal Insufficiency

- Adrenal insufficiency is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis.

- It is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency also in mineralocorticoids and adrenal androgens.
Adrenal insufficiency

- Adrenal insufficiency is classed as primary, secondary, or tertiary.
  - **Primary adrenal insufficiency** results from disease intrinsic to the adrenal cortex.
  - **Central adrenal insufficiency**, the collective name for the secondary and tertiary types
    - Secondary adrenal insufficiency results from pituitary disease that hampers the release of corticotropin.
    - Tertiary adrenal insufficiency results from the impaired synthesis or action of corticotropin-releasing hormone, arginine vasopressin, or both, from the hypothalamus, which in turn inhibits secretion of corticotropin.

Case 1

- 27 year woman presented with fatigue, weight loss and dizziness. She has noticed darkening of skin in last 6 months.
- She has lost 10 pounds in last 6 months
- BP – 100 / 60, HR - 104
- She had salt craving
- BMP – Sodium – 129, Potassium 5.3, Glucose -67

Clinical signs and symptoms of AI

- Constitutional symptoms including weakness, fatigue - 100%
- Anorexia - 100%
- Weight loss - 25%–100%
- Nausea - 35%–86%
- Vomiting - 25%–70%
- Constipation - 33%
- Diarrhea - 16%
- Abdominal pain - 34%
- Salt craving - 16%
- Amenorrhea - 25%
- Postural dizziness and syncope - 17%–20%
- Myalgia and arthralgia - 6%–17%
- Hypotension (systolic blood pressure <110 mm Hg) 88%–94%
- Hypoglycemia
- Psychiatric complaints including depression, apathy, psychosis, and pseudodementia
Hyperpigmentation in Primary Adrenal Insufficiency

Laboratory results in Primary AI

- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Raised urea
- Metabolic acidosis
- Hypercalcemia
- Raised thyroid-stimulating hormone
- Normocytic anemia
Diagnostic tests for Al

- Morning cortisol
- ACTH level
- Low aldosterone/high renin
- Low DHEA/DHEAS
- Etiology diagnosis
  - 21 hydroxylase antibodies

ACTH stimulation test

- ACTH stimulation test (Cosyntropin stimulation test)
  - Baseline ACTH and cortisol
  - 30 minutes cortisol after injection
  - 60 minutes cortisol after injection
- Medication: 250 µg (0.25 mg), cosyntropin (Cortrosyn, synthetic 1–24 ACTH) by IV or IM
- Sampling: Serum cortisol at baseline (0) and 30 or 60 minutes
- Interpretation:
  - Stimulated serum cortisol > 20 ug/dL (some reports of > 19 ug/dL)

Case 1

- ACTH – 400 pg/mL (9-52 pg/ml)
- Morning cortisol - 2.3 ug/dL
- ACTH stimulation test
  - Cortisol at 60 minutes – 5.9 ug/dL
### Causes of Primary Adrenal insufficiency

- **Autoimmune adrenalitis**
  - Isolated
  - Autoimmune Polyglandular syndrome APS type 1 (APECED)
- **Infectious adrenalitis**
  - Tuberculosis, AIDS, Fungal
- **Bilateral adrenal hemorrhage**
- **Bilateral adrenal metastases**
  - Lung, stomach, breast, and colon
- **Bilateral adrenal infiltration**
  - Primary adrenal lymphoma, amyloidosis, hemochromatosis
- **Bilateral adrenalectomy**
  - Unresolved Cushing’s syndrome, bilateral adrenal masses, bilateral pheochromocytoma
- **Genetic disorders**
  - Adrenoleukodystrophy or adrenomyeloneuropathy
  - Congenital adrenal hyperplasia

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**Adrenal hemorrhage**

[Image of adrenal hemorrhage]
Causes of Primary Adrenal insufficiency

- **Drug-induced adrenal insufficiency**
  - Anticoagulants (heparin, warfarin)
  - Tyrosine-kinase inhibitors (sunitinib)
  - Aminoglutethimide
  - Trilostane
  - Ketoconazole, fluconazole,
  - Etomidate
  - Phenytoin
  - Rifampicin, troglitazone

Causes of Secondary AI

- Space-occupying lesions or trauma
- Pituitary tumors
- Pituitary surgery or irradiation for pituitary tumors, tumors outside the HPA axis or leukemia
- Pituitary apoplexy
- Sheehan’s syndrome (peripartum pituitary apoplexy and necrosis)
- Infections or infiltrative processes
  - Lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, histiocytosis X, Wegener’s granulomatosis
Causes of Tertiary Adrenal Insufficiency

- **Space-occupying lesions or trauma**
  - Hypothalamic tumors (craniopharyngiomas or metastasis from lung or breast cancer)
  - Hypothalamic surgery or irradiation for CNS or nasopharyngeal tumors
  - Infections or infiltrative processes (lymphocytic hypophysitis, haemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener’s granulomatosis)
  - Trauma, injury (fracture of skull base)

- **Drug-induced adrenal insufficiency**
  - Suppression due to Glucocorticoid therapy
    - Systemic or topical
  - Mifepristone
  - Antipsychotics (chlorpromazine)
  - Antidepressants (imipramine)

Treatment

- Life long replacement with glucocorticoids and mineralocorticoids
  - Daily
  - Stress dosing
  - Medical alert/Card
  - Patient education
  - Treatment/Dosing
  - Clinical judgment
  - Over-replacement: weight gain, insomnia, edema
  - Under-replacement: weight loss, hyperpigmentation, nausea, lethargy, poor appetite
**Glucocorticoid and Mineralocorticoid treatment**

**Oral Glucocorticoid treatment**
- Hydrocortisone 15 – 25 mg daily
  - 2-3 divided doses
- Cortisone acetate 20 – 30 mg daily
  - 2 or 3 divided doses
- Prednisone 5 mg daily or BID
- Dexamethasone

**Oral Mineralocorticoid treatment**
- Fludrocortisone 0.05 – 0.2 mg in morning, salt intake without restriction

**Adrenal crisis**
- Parental injection (IV, IM or SC)
- Saline infusion
- Treatment of underlying causes

**Increased need (stress)**
- Hot climate
- Pregnancy
- Invasive medical procedures, operations, birth (often IV hydrocortisone)

**Assessment**
- Salt craving, dizziness, edema, blood pressure
- Electrolytes (potassium)
- Renin/renin activity (aiming at upper reference limits)

**Medical alert**
Put slide about the hydrocortisone kit

- Hydrocortisone 100 mg IM once
- Syringe


Adrenal fatigue

Case 2

- 48 y/o man with anxiety, palpitations and chronic fatigue
- No medication and no significant past medical history
- Stressful job
- BP – 130/76, HR – 76, BMI – 29.6
- Normal physical examination
- Integrative Wellness center
Adrenal Function in Chronic Stress

- AIDS patients
  - Adrenocortical adaptation to serious illness with shift away from androgen and mineralocorticoid production with perseveration of cortisol secretion

- PTSD patients
  - They have lower basal cortisol but demonstrate hyperresponsiveness to stimulation

- Chronic fatigue syndrome (CFS)
  - ACTH and cortisol response to insulin induced hypoglycemia was identical in control and CFS

Aguilera G et al, Endo Res 1996;22;433-
Golier A et al, Dep Res and Treat 2012
Cleare et al, JCEM 2001, 86;3545-

Case 2

- He was started on hydrocortisone 10 mg TID
  - No change in symptoms
  - Evaluated by another physician
    - ACTH stimulation test – adequate response
    - Hydrocortisone was discontinued
  - Two weeks later presented with groin and hip pain

Adrenal fatigue

- There is no clinical or experimental evidence that there is any state of cortisol deficiency that occurs after prolonged stress. In fact, the adrenal gland often remains hyperresponsive to stimuli following chronic stress.

- Accordingly, it seems very unlikely that there is a state of subclinical hypocortisolism that might benefit from glucocorticoid therapy

- There is no adrenal fatigue

Adrenal Incidentaloma

The adrenal incidentaloma is a public health challenge because these tumors are currently being detected in millions of people worldwide and their number is expected to grow in aging populations that have access to ever improving radiologic techniques.

Chidiac and Aron, 1997

Case 3

- 56 yo man with T2DM and hypertriglyceridemia presented to ER with nausea and vomiting
- He had CT scan of abdomen done in ER and was advised to follow up with PCP
- No significant family history
- Diagnosis – Gastroenteritis (fluids and anti-emetic)
- CT abdomen
  - 2 cm right adrenal lesion
  - < 10 Hounsfield units
- In PCP clinic
  - BP – 148/89, HR = 101

Adrenal Incidentaloma

- The adrenal gland is a common site of disease and can harbor a wide range of pathology.
- The prevalence of adrenal masses at CT is approximately 5%, comparable to the estimated prevalence in the general population of 3% to 7%.
- Frequency increases with age
  - <1 % at 20 years
  - >10 % at 70 years
- Most adrenal lesions are benign, most commonly nonfunctioning adenoma. However, the adrenal gland is also a common site of metastasis in oncologic patients.
**Adrenal Incidentaloma**

**MEDULLA**
- Pheochromocytoma
- Ganglioneuroma
- Ganglioneuroblastoma
- Neuroblastoma
- Carcinoma
- Cyst
- Pseudocyst
- Hematoma
- Hemorrhage

**CORTICAL**
- Adenoma (Cushing’s)
- Nodular hyperplasia
- Adrenal cortical carcinoma

**METASTASIS**
- Infection
- Granuloma

**Imaging phenotype of Adrenal Incidentaloma**

- **Benign appearance**
  - Unenhanced CT attenuation ≤10 Hounsfield units
  - CT contrast-medium washout ≥50% at 10 min

- **Suspicious appearance**
  - Unenhanced CT attenuation >10 Hounsfield units
  - CT contrast-medium washout <50% at 10 min

**Consider:**
- Repeating imaging at 6, 12, and 24 mo
- Repeating hormonal testing annually for 4 yr
- Surgery if mass is ≥4 cm in diameter

**Characteristics of Adrenal Incidentalomas on Imaging (Imaging Phenotype)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Usually &lt; 3 cm</td>
</tr>
<tr>
<td>Attenuation (density)</td>
<td>≤10 Hounsfield units</td>
</tr>
<tr>
<td>On enhanced CT</td>
<td></td>
</tr>
<tr>
<td>Vascularity on contrast-enhanced CT</td>
<td>Not highly vascular</td>
</tr>
<tr>
<td>Rapidity of washout of contrast medium</td>
<td>25-50% at 10 minutes</td>
</tr>
<tr>
<td>Appearance on MRI</td>
<td>Isointense relative to liver on T2-weighted image</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Usually stable over time or very slow (&lt;1 cm per year)</td>
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</table>

History and physical examination
Hormonal testing
• Overnight dexamethasone (1 mg) suppression test
• Frac. metanephrines and catecholamines in a 24-hr urinary specimen
• If HTN present, measure aldosterone and renin

Positive
Confirmatory tests
Surgery
Negative
Imaging phenotype

Case 3
• Endocrine evaluation
  • Overnight dexamethasone (1 mg) suppression test
    - Medication: 1 mg (in adults) dexamethasone at 11–12 PM
    - Sampling: Serum cortisol at 8 AM and dexamethasone level
    - Interpretation: Suppression of 8 AM serum cortisol to < 1.8 µg/dL effectively excludes Cushing’s syndrome. A cortisol level > 1.8 µg/dL merits further evaluation.
  • Fractionated metanephrines and catecholamines in a 24-hr urinary specimen, plasma metanephrines
  • If HTN present, measure aldosterone and renin with potassium

Adrenal Biopsy (Fine Needle Aspiration)
• Unless there is a known or possible extra-adrenal malignancy or suspicion of infection, there is little role for FNA. In those settings, however, it can be diagnostic and assist in the management plan
• FNA cannot distinguish benign from malignant adrenal cortical tissue
• Dangerous in pheochromocytoma
  • Hemorrhage
  • Hypertensive crisis
• Biochemical evaluation prior to considering biopsy
Pheochromocytoma

- Pheochromocytoma are chromaffin cell tumors
  - catecholamine producing
  - storage, release and metabolism (metanephrines, methoxytyramine)

PHEO = pheochromocytoma (adrenal)
PGLs = paraganglioma (extra adrenal)
Signs and Symptoms of Pheochromocytoma

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
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<tbody>
<tr>
<td>Headaches</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Tachycardia or reflex bradycardia</td>
</tr>
<tr>
<td>Sweating</td>
<td>++</td>
</tr>
<tr>
<td>Anxiety/hypervigil</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Tremulousness</td>
<td>Hypertension, paroxysmal</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>++</td>
</tr>
<tr>
<td>Pain in chest/abdomen</td>
<td>Weight loss</td>
</tr>
<tr>
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<td>++</td>
</tr>
<tr>
<td>Weakness/fatigue</td>
<td>Hypermetabolism</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Fasting hyperglycemia</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Paroxysms</td>
<td>Increased respiratory rate</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Decreased gastrointestinal motility</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>Psychosis (rare)</td>
</tr>
<tr>
<td>Seizures, grand mal</td>
<td>Flushing, paroxysmal (rare)</td>
</tr>
</tbody>
</table>

Differential Diagnosis for Pheochromocytoma

- Hyperadrenergic essential hypertension
- Baroreflex failure
- Thyrotoxicosis
- Anxiety, panic attacks
- Migraine or cluster headaches
- Autonomic hyperpyrexia
- Altered dopamine withdrawal
- Amphetamines
- Cocaine
- Alcoholism
- Ingestion of tyramine-containing foods or proprietary cold preparations while taking monoamine oxidase inhibitors
- Hypoglycemia, insulin reaction
- Paroxysmal tachycardia including paroxysmal tachycardia syndrome
- Angina pectoris or myocardial infarction
- Mitral valve prolapse
- Abdominal carcinofibromatous disection
- Cardiac ventricular conduction
- Renal parenchymal or renal artery disease
- Intestinal lesions, cerebral vessels, and hemorrhage
- Menopausal syndrome
- Lead poisoning
- Toxicity of pregnancy
- Unexplained shock
- Acute intermittent porphyria

Case Detection

- Resistant HTN
- Familial Syndromes
  - Family history of pheochromocytoma
  - Incidental adrenal mass
  - Paradoxical response to anesthesia or surgery
  - Hyperadrenergic spells
  - Onset of HTN at a young age < 20 years
  - Idiopathic dilated cardiomyopathy
  - History of gastrointestinal stromal tumor or pulmonary chondromas (Carney triad)
**Clinical suspicion of pheochromocytoma**

24 hour urine:
- Fract Metanephrines
- Fract Catecholamines

Plasma:
- Fract Metanephrines

Recheck during spell
- > 2 fold elevation above upper limit of nl in catecholamines and metanephrines or significant increase in frct plasma mets

Localization: Adrenal/abdominal MRI or CT scan

- I123 MIBG scan if 10 cm adrenal mass
- Paraganglioma

Reassess the diagnosis
- Consider: I123 MIBG scan
- PET scan, whole body MRI scan

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**Medications That May Increase Measured Levels of Fractionated Catecholamines and Metanephrines**

- Tricyclic antidepressants (including cyclobenzaprine Flexeril)
- Levodopa (Sinemet)
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines
- Buspirone and antipsychotic agents (not SSRI)
- Prochlorperazine
- Reserpine
- Withdrawal from clonidine
- Illicit drugs (e.g., cocaine, heroin)
- Ethanol
- Major physical stress (e.g., surgery, stroke, ICU)
- OSA syndrome

**Characteristics of Pheochromocytoma**

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<td>Vascularity on contrast-enhanced CT</td>
<td>Usually vascular</td>
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<td>Rapidly of washout of contrast medium</td>
<td>&lt;50% at 10 minutes</td>
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<td>Appearance on MRI</td>
<td>Markedly hyperintense in relation to liver on T2-weighted image</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Usually slow (0.5 cm to 1.0 cm per year)</td>
</tr>
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</table>

**References**

Hereditary pheochromocytoma

- Major susceptibility genes
  - VHL
  - MEN2
  - NF1
  - Succinate dehydrogenase gene family (SDHB and D)

- Minor susceptibility genes
  - TMEM127
  - SDHA and C
  - SDHAF2 (head and neck PGLs)
  - MAX
  - HIF2 alpha

von Hippel-Lindau disease (VHL gene)

- CNS hemagioblastoma 60-80%
- Retinal Hemagioblastoma 50-60%
- Pancreatic cysts 30.65%
- Kidney cysts and cancer 30.60%
- Pheochromocytoma 11-19%
- Endolymphatic sac tumor 2-10%

MEN 2 syndrome (RET gene)

- MEN 2A
  - Medullary thyroid cancer
  - Pheochromocytoma 50%
  - Hyperparathyroidism

- MEN 2B
  - Medullary thyroid cancer
  - Pheochromocytoma 50%
  - Marfanoid habitus
  - Multiple neuromas


Neurofibromatosis 1 (NF1 gene)

- Café-au-lait spots
- Axillary or inguinal freckling
- Cutaneous neurofibromas
- Plexiform neurofibroma
- Lisch nodules
- Optic glioma
- **Pheochromocytoma 0.5 – 5%**


Clinical algorithm for sequential gene testing for functional PHEO/PGL based on clinical and biochemical predictors.

Karasek et al. Journal of Human Hypertension (2013) 27, 141 – 147

**Table:**

<table>
<thead>
<tr>
<th>ALPHA AR</th>
<th>BETA AR</th>
</tr>
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<tbody>
<tr>
<td>Alpha₂</td>
<td>Beta₂</td>
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**Antagonists used in pheochromocytoma**

- Prazosin, Doxazosin, Terazosin
- Methyldopa
- Reserpine
- Labetalol

Cushing’s Syndrome

Mortality with Cushing’s syndrome (CS)

- Unknown 17%
- Cardiovascular 34%
- Other 17%
- Infectious disease 8%
- Persistent disease 8%
- Malignancy 9%
- Cerebrovascular 9%

Conditions associated with hypercortisolism without CS

- Some clinical features of CS may be present
  - Pregnancy
  - Depression
  - Alcohol dependence
  - Morbid obesity
- Unlikely to have any features of CS
  - Physical stress
  - Malnutrition
  - Hypothalamic amenorrhea

Cushing Syndrome

- ACTH dependent: 80% cases
- ACTH independent: 20% cases

Evaluation for CS

- Initial testing
  - 1 mg Dexamethasone suppression test
  - 24 hour Urine Free Cortisol
    - 2-3 collections
  - Late night Salivary cortisol
    - 1-2 samples
- Other tests
  - High dose Dexamethasone suppression test
  - CRH stimulation test
  - CRH-Dexamethasone test
  - Bilateral Inferior Petrosal Sinus sampling
    - Gold standard to differentiate ectopic from pituitary

Nieman et al. | Clin Endocrinol Metab. 2008; 91(s): 1526-340
Spurious Causes of Abnormal Dexamethasone Suppression Test Results

- **False Positive**
  - Increased metabolism: barbiturates, phenytoin, carbamazepine, primidone, rifampicin, aminoglutethimide
  - Increased cortisol-binding globulin: pregnancy, oral estrogens, tamoxifen
  - Malabsorption
  - Pseudo-Cushing’s states

- **False Negative**
  - Reduced metabolism: high-dose benzodiazepines, indomethacin, liver disease

**Primary Hyperaldosteronism**
Hyperaldosteronism

- **Primary Hyperaldosteronism (PA)**
  - Primary adrenal production of excess aldosterone independent of renin

- **Secondary Hyperaldosteronism**
  - Secondary adrenal production of aldosterone because of excessive renin release:
    - High aldosterone and non-suppressed Plasma renin activity
      - Renovascular HTN
      - Coarctation of the aorta
      - Renin producing tumor

**Primary Hyperaldosteronism (PA)**

- Aldosterone-producing adenomas, which cause 80% of Conn’s syndrome, are usually smaller than 2 cm with a significant portion less than 1 cm.
- Adrenal hypersecretion of aldosterone independent of renin
  - HTN
  - Increased Aldosterone levels
  - Low plasma renin activity (PRA) levels
- Two most common causes
  - Unilateral aldosterone producing adenoma (APA)
  - Bilateral idiopathic hyperaldosteronism (IHA)
- PA is the most common cause of secondary hypertension (5-10% of all hypertensive)

**When should you test**

- Increase BP and hypokalemia
- Resistant hypertension (3BP drugs and poor control)
- Severe hypertension
  - (SBP > 160 mm Hg or DBP > 100 mm Hg)
- Hypertension and incidental adrenal mass
- Onset of hypertension at a young age (eg < 30 years)
- Whenever performing a secondary hypertension evaluation (e.g. when testing for renovascular disease or pheochromocytoma)
Case detection

- Morning 8 – 10 am ambulatory paired plasma aldosterone concentration (PAC) and plasma renin activity (PRA)
- It is optimal to restore potassium to normal before performing the tests
- May be performed while the patient is on BP medications and without posture stimulation
- Medications contraindicated (spironolactone and eplerenone) and high dose amiloride. Discontinue the medications for at least 6 weeks if clinically feasible

Unilateral aldosterone producing adenoma (APA)
Bilateral idiopathic hyperaldosteronism (IHA)

Subtype-Directed Treatment for 1° Aldo

Other Antihypertensive Agents
- Amlodipine
- HCTZ
- ACE-I
- ARB
- CCB

Mineralocorticoid-Receptor Antagonist (MR-A)
Selective MR-A: Eplerenone
Nonselective MR-A: Spironolactone

Laparoscopic Adrenalectomy
Thank you