Diagnosis and Management of Adrenal Disorders

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Adrenal Disorders

Adrenocortical Hypofunction
- Addison’s disease
- Hypoaldosteronism

Adrenocortical Hyperfunction
- Cushing’s syndrome
- Hyperaldosteronism

Adrenal medulla hyperfunction
- Pheochromocytoma

Adrenal Incidentaloma
- Unsuspected adrenal mass found on imaging
Adrenocortical Hypofunction

Primary hypofunction
- Addison’s disease
- Aldosterone deficiency

Secondary hypofunction
- Secondary adrenal insufficiency
- Hyporeninemic hypoaldosteronism
The hypothalamo-pituitary-adrenal axis in primary and secondary adrenocortical insufficiency

**Primary adrenocortical insufficiency**
- Hypothalamus
  - CRH
  - ACTH
  - Adrenal
  - Cortisol

**Secondary adrenocortical insufficiency**
- Hypothalamus
  - CRH
  - ACTH
  - Adrenal
  - Cortisol
Causes of Addison’s Disease

- Autoimmune
  - TB, fungal, HIV, others
- Infectious
  - TB, fungal, HIV, others
- Metastatic cancer
- Adrenal hemorrhage or infarction
- Drugs
  - Ketoconazole, rifampin, phenytoin, flucanazole, others
- Hereditary disorders
Addison’s Disease from Autoimmunity

May be associated with other autoimmune processes

Polyglandular autoimmune syndromes

Schmidt Syndrome - primary adrenal and primary thyroid deficiencies

Most common

Spares the medulla
## Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
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<tr>
<td>Anorexia and weight loss</td>
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<tr>
<td>Dehydration and hypotension</td>
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<tr>
<td>Nausea &amp; vomiting</td>
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<tr>
<td>Hyponatremia and hyperkalemia</td>
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<tr>
<td>Hypoglycemia</td>
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<td>Hyperpigmentation, vitiligo, or both</td>
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Addison’s Disease

- Often presents as a medical emergency
- Treatment should not be delayed awaiting diagnosis
- Labs can be obtained even as therapy is started (with caveats)
Diagnosis of Addison’s Disease

Low cortisol and high ACTH confirms primary adrenal insufficiency

Cortisol results available quickly

ACTH results not be available for days
Emergency Treatment

Patient is treated with 4mg of dexamethasone and IV fluids while a rapid ACTH (cortrosyn) test is performed.

Adrenal suppression from glucocorticoids takes several days to develop.

Dexamethasone does not react with the cortisol assay, so it does not confuse the results.
Rapid ACTH stimulation test

**Baseline cortisol (and ACTH)**

**Administer cosyntropin 250 µg (synthetic ACTH)**

**Cortisol drawn 30 min. and 1 hour later**

- Any reading > 18.5 µg/ml is a normal response
- Abnormal responses occur with both primary and secondary adrenal insufficiency
Etiologies of Secondary Adrenal Insufficiency

- Hypothalamic or pituitary tumors
  - Produce long-term suppression of the hypothalamic/pituitary/adrenal axis
  - If not tapered appropriately, adrenal insufficiency occurs
  - The most common cause of adrenal insufficiency

- Isolated ACTH deficiency

- Exogenous glucocorticoids
  - Produce long-term suppression of the hypothalamic/pituitary/adrenal axis
  - If not tapered appropriately, adrenal insufficiency occurs
  - The most common cause of adrenal insufficiency
Differences from primary adrenal insufficiency

- Mineralocorticoid deficiency uncommon
- No hyperpigmentation
### Treatment of Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Status</th>
<th>Hydrocortisone</th>
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<tbody>
<tr>
<td>Normal Daily</td>
<td>15 to 30 mg PO in 2-3 doses</td>
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<tr>
<td>Minor stress</td>
<td>30-50 mg PO in 2-3 doses</td>
</tr>
<tr>
<td>Moderate stress</td>
<td>45-75 mg PO or IV in 3-4 doses</td>
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<tr>
<td>Severe stress</td>
<td>150-200 IV in 4 doses</td>
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Hypoaldosteronism

Characterized by hyperkalemia (elevated potassium)

Should be considered in any patient with persistent hyperkalemia in whom there is no obvious cause.
Non-aldosterone Causes of Hyperkalemia

**Advanced renal failure**
- Easily diagnosed with BUN and creatinine

**Marked volume depletion (actual or effective)**
- Diminished sodium and water delivery to the distal site of potassium secretion
- Most often occurs in patients with severe heart failure
Causes of Hypoaldosteronism

- Aldosterone deficiency
- Hyporeninemic hypoaldosteronism
- Aldosterone resistance
Aldosterone deficiency

- Addison’s disease
- Congenital adrenal hyperplasia (CAH)
- Heparin and low molecular weight heparin
  - Adrenal hemorrhage and direct suppression
Hyporeninemic hypoaldosteronism

Renal disease
- Characteristically diabetes

Volume expansion
- Acute glomerulonephritis

Misc.
- ACE inhibitors, NSAIDS, cyclosporine, HIV
Aldosterone resistance

- Amiloride
- Triamterene
- Spironolactone
Cushing’s Syndrome

glucocorticoid excess
Cushing’s Syndrome

Clinical Features

- Progressive obesity (classically truncal)
- Skin atrophy, easy bruisability, striae, fungal infections, hyper-pigmentation, hirsutism, acne
- Menstrual irregularities
- Glucose intolerance or diabetes
- Hypertension, hypokalemia
- Thromboembolisms
- Psychological changes
Glucocorticoid Excess

Cushing's Syndrome
- The clinical manifestations of glucocorticoid excess
- Includes glucocorticoid excess from any source

Cushing's disease
- Glucocorticoid excess specifically due to ACTH secretion from a pituitary adenoma
- Does cause Cushing’s Syndrome
Does the Patient have a Disease?

Serum cortisol may be secondarily elevated from many causes besides excess ACTH production or autonomous adrenal gland secretion.

Evaluation can be difficult.

Before invasive or imaging studies, it is important to perform screening studies.
Screening for Cushing's Syndrome

- Low dose dexamethasone suppression
- Outpatient screening only
- Test has a low false negative rate
- High false positive result if done in the hospital!!
Low dose dexamethasone suppression

1.0 mg dexamethasone 10-11 pm

- Checking AM dexamethasone level confirms absorption and adherence

8 am cortisol

- serum cortisol should be < 5 μg/dL
- salivary cortisol should be < 2 n/mL
Diagnosis of Cushing’s syndrome

Urine free cortisol (24 hour urine collection)
- Positive if more than 3 times upper normal
- Indeterminate if 1-3 times upper normal
- If indeterminate, check late evening serum or salivary cortisol (lack of diurnal variation)
Etiologies of Cushing's Syndrome

ACTH dependent
- Pituitary (Cushing's Disease)
- Ectopic ACTH

ACTH independent
- Adrenal adenoma
- Adrenal carcinoma
- Exogenous glucocorticoids
Hypothalamic-pituitary (Cushing's Disease)

- ACTH is usually elevated, but can be "normal" if their cortisol was high.
- ACTH can be suppressed with higher levels of glucocorticoids.
- A pituitary tumor may not be visible in ½ the cases.
- Ectopic ACTH secretion by some carcinoid tumors can also exhibit ACTH suppressibility.

- Low and high dose protocols.
- May need inferior petrosal vein sampling to confirm the source is pituitary.
- Only an issue for failure to localize pituitary adenoma and unsuspected, occult carcinoid.
Ectopic ACTH

- ACTH secretion by a tumor (usually several times the upper limit of normal)
- Values can overlap with Cushing’s disease early in the course of the cancer
- Ectopic ACTH does not respond to dexamethasone suppression (unless carcinoid)
ACTH is suppressed by the elevated cortisol

Adrenal adenoma or carcinoma

Exogenous glucocorticoids (most common)

ACTH Independent Cushing’s Syndrome
Exogenous glucocorticoids

ACTH suppression may last for days to weeks depending on the dose and duration

May present with adrenal insufficiency if taken off glucocorticoids too quickly

Don’t forget joint and back injections

Patient may forget or not realize steroids were injected
Levels of ACTH in Cushing’s Syndrome

- Cushing's Disease - Normal to high ACTH
- Ectopic ACTH – typically a very high ACTH
- Exogenous steroids or adrenal etiology - suppressed ACTH
Hyperaldosteronism

Primary
- Autonomous production by adrenals

Secondary
- Stimulation of adrenal production from other causes
Primary Hyperaldosteronism

Autonomous adrenal production
- Adenoma - 75-85% of cases
- Bilateral hyperplasia - 15-25% of cases
- Carcinoma - <1% of cases

Clinical manifestations
- Hypertension - one of the potentially curable forms of hypertension
- Hypokalemia
Diagnosis of Primary Hyperaldosteronism

Plasma aldosterone concentration (ng/dl) to plasma renin activity (ng/ml per hour) ratio (PAC/PRA ratio)

- Normal subjects and patients with essential hypertension is 4 to 10
- More than 20 in most patients with primary aldosteronism

Failure of serum or urine aldosterone to suppress with a high salt load

- Usually with oral salt loading
- Can be with IV
Secondary Hyperaldosteronism

- **Physiologic response to various conditions of reduced effective arterial blood volume**
  - Inadequate volume or low perfusion

- **Extrarenal**
  - Hypovolemia
  - Edematous states

- **Renal**
  - Impaired renal tubular absorption of Na and Cl
  - Accelerated hypertension
  - Renovascular lesions
  - Renin-secreting neoplasms (rare)
Pheochromocytoma

A rare disease, probably occurring in less than 0.2 percent of patients with hypertension.

About half have paroxysmal hypertension and the other half appear to have essential hypertension.

Worth diagnosing because it can be life-threatening and is a treatable form of hypertension.
Clinical features of pheochromocytoma

Classic triad of symptoms
- Episodic headache
- Sweating
- Tachycardia

Symptoms are common in the general population

Not all patients have the three classic symptoms, but most have two of the three
Other clinical features

- Pallor
- Orthostatic hypotension (may reflect a low plasma volume)
- Visual blurring, papilledema
- Weight loss
- Hyperglycemia
- Psychiatric disorders
- Dilated cardiomyopathy
Diagnosis

Clinical suspicion

- Hypertension and symptoms
- Associated with MEN IIA and MEN IIB

Biochemical confirmation

- Always precedes imaging

Localization

- Solitary adrenal lesion in 90% of cases
Biochemical confirmation

Plasma values
- High false positive results
- Low false negative
- Use for lower suspicion

24 hour urine
- Free catecholamines (epinephrine and norepinephrine)
- Metanephrines
- VMA (vanillylmandelic acid)
- Use for higher suspicion or MEN syndromes
Results of urine studies

Values should be at least twice the upper limits of normal

There are multiple drugs and foods that interfere with the metabolite assays

| Special diet | Discontinue interfering medications (look up before starting urine collection) | Labetalol is the only hypertensive interfering with fractionated catecholamines |

- Labetalol is the only hypertensive interfering with fractionated catecholamines
10% are extra-adrenal
95% are within the abdomen
On MRI, T2-weighted images appear hyperintense

Can use CT or MRI

Non-functional adrenal tumors are common

See adrenal incidentaloma below
Localization should not precede making a biochemical diagnosis
Other imaging techniques

- Norepinephrine analogue
  - MIBG scan

- Increased uptake of glucose
  - Fluorodeoxyglucose PET or FDG-PET

- Somatostatin receptor
  - Octreotide
  - Dotatate PET scan – most sensitive
For reference: not on test
Adrenal Incidentaloma

- Found on imaging studies done for other reasons
  - Unsuspected

- Asymptomatic adrenal masses
  - 2-3% of >50 year olds
  - Up to 7% of those over 70 years

- Up to 10% are subclinical
  - Functional without clinical symptoms or signs

- Differential Dx
  - Primary - benign or malignant
  - Metastatic or infectious
Assessment of incidental adrenal mass

- H&P to look for evidence of malignancy or adrenal hormone excess

- Most patients with cancer metastatic to adrenals have evidence of cancer elsewhere

- Imaging characteristics may provide clues
Biochemical Evaluation

- Functional tumors are can be subclinical, so biochemical evaluation is needed

- Check for cortisol, aldosterone, DHEAS, and catecholamine excess
Size of non-functional adenomas:

- <3.5-4 cm are usually followed with imaging in 6-12 months.
- >6 cm are usually resected.
- Tumors 4-6 cm may go either way depending on presence or absence of suspicious features on imaging.
Endocrinology Basics

Endocrine systems are dynamic.
- Individual lab values outside the “normal” range may be entirely appropriate depending on the clinical status

Normal is a relative value
- If a hormone is low, its regulating hormone should be elevated
- If a hormone is elevated, its regulating hormone should be low

Avoid the temptation to jump to imaging until you know the patient has a disease.
- Imaging can be performed quicker than biochemical testing
- Non-functioning, benign tumors are common in endocrine organs
- You may develop tunnel vision and misdiagnose
“Don’t believe everything you read on the Internet just because there’s a picture with a quote next to it.”

—Abraham Lincoln