4:25 – 5:05pm

Pituitary and Adrenal Dysfunction: How to Screen and Manage

**SPEAKER**
Whitney Woodmansee, MD

---

**Presenter Disclosure Information**

The following relationships exist related to this presentation:

- Whitney Woodmansee, MD: Principal investigator for Ispen and Novo Nordisk.

**Off-Label/Investigational Discussion**

- In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

---

**Adrenal & Pituitary Disease**

Whitney W. Woodmansee MD
James V. Hennessey MD, FACP

---

**The Case**

- 56 y.o. man presents with a 4 month history of fatigue, 2 month history of anorexia and weight loss, 1 week history of postural symptoms upon arising from a sitting position

- **PMHx:**
  - **Hypogonadism:** Low testosterone levels noted four years ago and treated by a urologic colleague with testosterone gel. Stopped when no effect noted
  - **Hypercholesterolemia** noted 6 years ago and treated with diet

- **ROS:** Fatigue, cold intolerance, anorexia, 15 lb weight loss, erectile dysfunction, muscle cramps

---

**The Initial Evaluation**

- **BP 101/60, Pulse 92 sitting, 80/40, P 115 erect**
- **Temp 99.1, RR 16**
- **Height 70”, Weight 135 lbs, BMI 19.4 kg/m2**
- **Gen: Pale appearing, appears chronically ill**
- **PERRLA, EOMI, Nares /OP clear**
- **Thyroid: Palpable firm goiter, 35 grams, bossulated**
- **CV: RRR**
- **Pulm: Clear to A&P**
- **Abd: BS+, soft, diffusely mildly tender, no rebound, no masses**
- **Extremities: Thin, pate, without C/C/E**
- **Neuro: CNs: Possible temporal anopsia, otherwise nonfocal**

---

**Initial Laboratory Evaluation**

- **Medications at time of evaluation: None**
- **Laboratory testing:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 PM</td>
<td>BUN</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Cr.</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Cortisol</td>
<td>1.2 mcg/dl</td>
</tr>
</tbody>
</table>

- **ACTH Stimulation test:**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Cortisol</th>
<th>ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.1</td>
<td>6.2</td>
</tr>
<tr>
<td>30/60 minutes</td>
<td>1.2/1.5</td>
<td></td>
</tr>
</tbody>
</table>

- **Diagnosis:** Central Adrenal Insufficiency
Adrenal Physiology

Zona glomerulosa: Aldosterone
Zona fasciculata: GCC & Androgens
Zona reticularis: GCC & Androgens

Catecholamines

Hypothalamus ➔ CRH ➔ Anterior Pituitary ➔ ACTH ➔ Cortisol ➔ Adrenal

Adrenal Disorders

Adrenal Hyperfunction
- Cushing’s syndrome
  - Excess glucocorticoids
- Hyperaldosteronism
  - Excess mineralocorticoids
- Congenital Adrenal Hyperplasia
  - Excess Androgens
- Pheochromocytoma
  - Excess catecholamines

Adrenal Hypofunction
- Primary adrenal insufficiency
  - Low Cortisol/Aldo
  - Elevated ACTH
- Central adrenal insufficiency
  - Low ACTH
  - Low Cortisol

Adrenal Disorders

Adrenal Hyperfunction

Adrenal Hypofunction

Adrenal Insufficiency

Clinical Features
- Weakness
- Fatigue
- GI distress
- Salt craving
- Weight loss
- Physical exam:
  - hypotension
  - vitiligo
  - hyperpigmentation
- Lab abnormalities
  - Hyponatremia
  - Hyperkalemia
  - Hypoglycemia
- Other autoimmune disorders
- Adrenal calcifications

Primary Adrenal Insufficiency (Addison’s Disease):
- Autoimmune adrenalitis (80%)
- Infections: TB, HIV, CMV, fungus
- Metastatic disease
- Rare:
  - Adrenal hemorrhage, infarction
  - Infiltrative diseases: sarcoid, amyloid, hemochromatosis
  - Medications: enzyme inhibitors, cytotoxic agents
  - Surgery, XRT

Secondary (Central) Adrenal Insufficiency:
- Hypothalamic (tertiary)
  - Glucocorticoid therapy
    - 20+ mg Prednisone >5 days
    - >5 mg/day for >1 month
    - 12+ months may elapse before full HPA axis recovery following prolonged CG Rx!
- Tumors
- Radiation

Pituitary (secondary)
- Tumors
- Radiation
- Infiltrative diseases
- Infarction / Apoplexy
- Trauma

Diagnosis
- Baseline labs: Cortisol, ACTH, +/- Aldosterone
- Gold Standard: ACTH (Cortrosyn®) stimulation test
  - Low dose 1 mcg test
  - High dose (standard) 250 mcg test
- Protocol:
  - Baseline cortisol +/- aldosterone
  - Give ACTH I.V. or I.M.
  - Re-measure cortisol (+/- aldosterone) at 30 and 60 minutes
- CRH tests
- Imaging based on diagnosis

Adrenal Insufficiency

Secondary (Central) Adrenal Insufficiency:
- Hypothalamic (tertiary)
  - Glucocorticoid therapy
    - 20+ mg Prednisone >5 days
    - >5 mg/day for >1 month
    - 12+ months may elapse before full HPA axis recovery following prolonged CG Rx!
- Tumors
- Radiation

Pituitary (secondary)
- Tumors
- Radiation
- Infiltrative diseases
- Infarction / Apoplexy
- Trauma

Diagnosis
- Baseline labs: Cortisol, ACTH, +/- Aldosterone
- Gold Standard: ACTH (Cortrosyn®) stimulation test
  - Low dose 1 mcg test
  - High dose (standard) 250 mcg test
- Protocol:
  - Baseline cortisol +/- aldosterone
  - Give ACTH I.V. or I.M.
  - Re-measure cortisol (+/- aldosterone) at 30 and 60 minutes
- CRH tests
- Imaging based on diagnosis
Adrenal Insufficiency

Diagnosis

Laboratory Interpretation:
- ACTH stimulation test:
  - Stimulated cortisol > 18-20 mcg/dL considered a normal response to the standard 250 mcg ACTH test

High ACTH ➔ Primary Adrenal Insufficiency

Low or "normal" ACTH ➔ Secondary Adrenal Insufficiency

Acute Adrenal Crisis:
- Hydrocortisone 50-100 mg IV q 8 hrs
- Intravenous fluids (appropriate for BP)
- Rule out precipitating factors:
  - trauma
  - infection
  - dehydration
- Taper glucocorticoids as quickly as clinical condition allows
  - To maintenance dosage if AI documented
  - Off if ACTH stimulation test normal

Chronic Treatment:
- Hydrocortisone or prednisone
  +/- mineralocorticoid (usually only in primary AI)
- Patient education:
  - Stress / illness dosing of steroids
  - Medic alert jewelry
  - Family education
- Lowest dose possible to control symptoms
  - Avoid complications
    - Cushing’s syndrome, osteoporosis, DM

Back to the Patient
- Patient started on hydrocortisone and immediately felt better
  - Energy improved
  - Orthostatic hypotension symptoms resolved
  - GI symptoms disappeared
- Since his diagnosis was consistent with central adrenal insufficiency, a pituitary MRI was obtained to rule out a structural lesion
- Hydrocortisone dose tapered to the lowest dose to control his symptoms and avoid complications
  - Hydrocortisone 15mg in am / 5 mg in afternoon
  - No edema, hypertension, weight gain, changes in body composition

Approach to Pituitary Disorders: Incidental or Clinically Evident

Evaluate:
- Mass effects
- Pituitary hyperfunction
  - Baseline and “Suppression tests”
- Pituitary hypofunction
  - Baseline and “Stimulation tests”

Anterior Pituitary
- Sellar Masses
  - Pituitary Adenoma
    - Mass effect
    - Hyperfunction
  - Hypofunction
  - Apoplexy
  - Hypopituitarism

Posterior Pituitary
- Overproduction of AVP
  - Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)
- Underproduction of AVP
  - Diabetes Insipidus
    - Central (hypothalamic)
    - Nephrogenic
Differential Diagnosis of Sellar/Parasellar Lesions

**Benign Tumors**
- Pituitary adenoma
- Meningioma

**Cell Rest Tumors**
- Craniopharyngioma
- Rathke’s cleft cyst
- Epidermoid
- Lipoma
- Colloid cyst

**Primitive Germ Cell Tumors**
- Germinoma
- Teratoma
- Dysgerminoma
- Oligodendroglioma
- Epidermoid

**Granulomatous, Infectious, and Inflammatory Processes**
- Lymphocytic hypophysitis
- Abscess
- Sarcoidosis
- Tuberculosis
- Eosinophilic granulomatosis
- Mycoses

**Metastatic Tumors**
- **Granulomatous, Infectious, and Inflammatory Processes**
- Lymphocytic hypophysitis
- Abscess
- Sarcoidosis
- Tuberculosis
- Eosinophilic granulomatosis
- Mycoses

**Vascular Lesions**
- Empty sella syndrome
- Arachnoid cyst

**Hematologic Malignancies**
- Leukemia
- Lymphoma

**Miscellaneous**
- Empty sella syndrome
- Arachnoid cyst

**Pituitary Adenomas: Epidemiology**

- Pituitary adenomas are the 3rd most common brain tumor
- They account for 10-15% of all intracranial tumors
  - MRI studies: 14.4% incidental finding
  - Autopsy series: 12-22.5% incidental finding
- They are classified according to size
  - Microadenomas: <10mm
  - Macroadenomas: >10mm

**Pituitary Physiology**

**Anterior Pituitary**
- Hypothalamic Releasing Hormone
- Anterior Pituitary Hormone
- Target Organ

**Posterior Pituitary**
- Hypothalamus: Supraoptic and Paraventricular nuclei
- Axons
- AVP
- Oxytocin

**Pituitary Patient Evaluation**

**History:**
- Question regarding endocrine hypo or hyper function. Think of anterior & posterior pituitary function

**Hypofunction:**
- Hypothyroidism
- Hypogonadism
- Adrenal insufficiency
- GH Deficiency

**Hyperfunction:**
- Hyperthyroidism
- Prolactin excess
- Cushings’ syndrome
- GH excess

**Neurological symptoms:**
- Headaches, visual disturbance
- Visual field testing essential

**Pituitary Axis Laboratory Tests**

**Thyroid**
- TSH AND Free T4 (sometimes need Total T4, T3RU)

**Reproductive**
- Prolactin (with dilution if macroadenoma)
- FSH, LH AND Testosterone (men), or Estradiol (women)

**Growth Hormone**
- IGF-I, GH
- Critical to assess prolactin prior proceeding to surgery

**Adrenal**
- ACTH AND Cortisol
- Extra tests required if GH or ACTH excess is suspected

**Back to the Patient**

- PMD office faxes over the following laboratory tests:

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>Prolactin</th>
<th>LH</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 (low)</td>
<td>88 (high)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Laboratory Interpretation:**
- Hyperprolactinemia
- Central Hypogonadism
Clinical Presentation of Hyperprolactinemia

• Galactorrhea
• Hypogonadism
  – Amenorrhea / menstrual irregularities
  – Infertility
  – Erectile dysfunction
  – Growth arrest / delayed puberty
• Hirsutism
• Gynecomastia
• Mass effects if tumor is large

DDx: Hyperprolactinemia

• Physiologic States:
  – Pregnancy, Lactation, Exercise, Stress, Sleep
• Medications
• Primary Hypothyroidism
• Hypothalamic-pituitary stalk damage
  – Radiation, infarctions, cysts, tumors, trauma
• Pituitary tumor (prolactinoma + others)
• Systemic Disorders:
  – Neurogenic chest wall lesion, Renal failure, Cirrhosis, Seizures
  – Ectopic production - ovarian tumors
  – Idiopathic
  – Macroprolactinemia

Medications and Hyperprolactinemia

Common
• Neuroleptics/Antipsychotics
  – Phenothiazines, haloperidol, resperidone, olanzepine
• Estrogens
• Antihistamines
• Cholinergic agonists
• Anesthetics
• Anticonvulsants
• GI motility agents:
  – Cimetidine, metoclopramide

Less Common
• Antihypertensives
  – Methyldopa, reserpine, verapamil
• Anti depressants
  – Tricyclics, SSRI’s (minimal)
• Opiates
• Neuropeptides
• DA receptor antagonists
• DA synthesis inhibitors
  – Methyldopa

Prolactinoma Facts

• Prevalence: 3-5% in autopsy studies
• Clinical Incidence: 1-2 per million per year
• Accounts for 30-40% of pituitary tumors
• Accounts for 5% of all intracranial tumors
• More common in women (3 fold higher) than men
• Premenopausal women usually present earlier with clinical symptoms and microadenomas
• Post menopausal women and men usually present later with macroadenomas

Prolactinomas: Treatment Options

General Treatment Options:
• Medical Therapy with DA agonists
  – Cabergoline (preferred), Bromocriptine
• Transsphenoidal resection
  – Second line therapy in most cases
  – Consider for intolerance or resistance to DA agonist Rx
• Radiation (Third line therapy)
  – Residual tumor post-operatively
  – Resistant or aggressive tumors

Prolactinomas: Medical Therapy

Medical Therapy with DA agonists
• Cabergoline (preferred), Bromocriptine
• Outcome measures:
  – Literature review: The Endocrine Society (2011)
  – Outcomes with DA agonists (median, range)
  – Reduction in tumor size: 62% (20-100%)
  – Resolution of VF deficits: 67% (33-100%)
  – Resolution of amenorrhea: 78% (40-100%)
  – Resolution of infertility: 53% (10-100%)
  – Resolution of galactorrhea: 86% (33-100%)
  – Normalization of prolactin level: 68% (40-100%)
Prolactinomas: Medical Therapy

Endocrine Society Guidelines (2011)
- Recommend not treating asymptomatic microprolactinomas with DA agonists
  - Suggest DA agonist or estrogen if amenorrhea
- Recommend not using DA agonists in asymptomatic medication induced hyperprolactinemia
  - Stop medication or treat hypogonadism


Duration of Medical Therapy
- Answer: “It depends”
- Long term Rx generally for macroadenomas
- May be able to stop in smaller tumors responsive to the DA agonist
  - Better response in patients with idiopathic hyperprolactinemia, cabergoline use, longer duration of treatment
  - Typically treat 2 years and if no visible tumor and prolactin normal, can attempt trial of stopping the DA agonist


Prolactinomas: Indications for Surgery
- Resistance to Dopamine Agonists
- Intolerance of Medical Therapy
- Cystic Adenomas
- CSF Rhinorrhea
- Apoplexy
- ? Restoration of fertility ?


Laboratory Interpretation:
- Hyperprolactinemia
- Central Hypogonadism
- Primary Hypothyroidism

Back to the Patient
- Further pituitary function evaluation:

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>88 (low)</td>
</tr>
<tr>
<td>FSH</td>
<td>1.3</td>
</tr>
<tr>
<td>LH</td>
<td>1.8</td>
</tr>
<tr>
<td>Prolactin</td>
<td>75 (high)</td>
</tr>
<tr>
<td>TSH</td>
<td>22 (high)</td>
</tr>
<tr>
<td>FreeT4</td>
<td>0.23 (low)</td>
</tr>
<tr>
<td>IGF-I</td>
<td>114 (normal)</td>
</tr>
<tr>
<td>GH</td>
<td>0.5 (normal)</td>
</tr>
</tbody>
</table>

Case Summary
- This patient has a nonfunctioning pituitary adenoma
- His hormonal abnormalities included:
  - Central adrenal insufficiency
  - Primary hypothyroidism (independent of adenoma)
  - Hyperprolactinemia – exacerbated by hypothyroidism, and/or due to “Stalk effect”
  - Central hypogonadism- due to hyperprolactinemia or gonadotrope dysfunction from tumor compression

Treatment Course
- Levothyroxine replacement initiated
- Labs rechecked 6 weeks later

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>180 (low)</td>
</tr>
<tr>
<td>FSH</td>
<td>1.4</td>
</tr>
<tr>
<td>LH</td>
<td>1.7</td>
</tr>
<tr>
<td>Prolactin</td>
<td>33 (minimally elevated)</td>
</tr>
<tr>
<td>TSH</td>
<td>2 (normal)</td>
</tr>
<tr>
<td>FreeT4</td>
<td>1.2 (normal)</td>
</tr>
</tbody>
</table>

Does this patient have a prolactinoma?
No!!

Nonfunctioning Adenomas

- Appear hormonally inactive
  - Can secrete α subunit, β subunit or intact gonadotropins
- One third of all pituitary tumors
- May present incidentally
- Macroadenomas may present mass effect symptoms only
- Some patients with large tumors can present with hypopituitarism (one or more hormonal deficits)
- Treatment of choice for macroadenomas usually surgery

Perioperative Management

Preoperative Evaluation:
- Assess pituitary function:
  - Replace as needed
  - Thyroid & glucocorticoids
  - Stress dosing glucocorticoids if necessary

Early Inpatient Management:
- Assess for complications:
  - Neurologic status
  - Endocrine
    - Diabetes insipidus
    - SIADH
    - Adrenal insufficiency

Long Term Management:
- Patients typically evaluated 1, 6, 12 weeks postoperatively
- MRI typically repeated at 12 week visit to serve as new baseline
- Annual follow-up recommended or as dictated by clinic status
- MRI
- Long term assessment of hormonal status and tumor recurrence required

Pituitary Adenoma

Therapeutic Considerations

- Treating symptoms related to mass effects
  - Restoration or preservation of vision
  - Neurologic improvements – cranial nerves, headaches
- Correcting pituitary hyperfunction
  - Aim for biochemical cure
- Medical therapy for hormonal replacement

Hypopituitarism

Management

- Treatment based on correcting hormonal deficiencies
  - Thyroid – levothyroxine (TSH cannot guide Rx, FT4 upper nl)
  - Adrenal – HCC or prednisone. Use lowest dose possible
    - Patients with central adrenal insufficiency rarely need mineralocorticoid replacement.
  - Gonadal – Men require testosterone
    - Women may require HRT (OCP)
  - Growth hormone – Can treat with rhGH
  - Prolactin – no replacement available or required
  - Posterior pituitary – Desmopressin (DDAVP)
- Medical Alert Jewelry

Adrenal Insufficiency

Management

- Treatment with glucocorticoid replacement using the lowest dose to control symptoms
- Mineralocorticoid replacement typically only required in primary adrenal insufficiency
- Use stress dose steroids when necessary, avoid over-replacement and minimize side effects

Pituitary Disease Summary

“Take Home” Messages

1. When evaluating patients with pituitary disorders, let pituitary physiology be your guide to appropriate evaluation:
   - Mass effects (headache, visual dysfunction)
   - Pituitary hyperfunction
     - GH (Acromegaly)
     - ACTH (Cushing’s disease – hypercortisolism)
     - Prolactin (galactorrhea, menstrual disorders, erectile dysfunction)
     - TSH (hyperthyroidism)
   - Pituitary hypofunction – deficiency in all hormonal systems possible
2. Treatment is aimed at restoring normal pituitary function and can include: surgery, hormonal replacement, medications

Adrenal Insufficiency Summary

“Take Home” Messages

1. Clinical presentation may vary in severity and include nonspecific symptoms
2. Diagnosis confirmed by ACTH (Cortrosyn®) stimulation test
3. It is important to differentiate primary vs. central adrenal insufficiency (evaluate for anatomic lesions if central)
4. Treatment with glucocorticoid replacement using the lowest dose to control symptoms
5. Mineralocorticoid replacement typically only required in primary adrenal insufficiency
6. Use stress dose steroids when necessary, avoid over-replacement and minimize side effects