10:45 – 11:45am

Pituitary and Adrenal Dysfunction: How to Screen and Manage

SPEAKER
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1. Adrenal & Pituitary Disease

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2. 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

3. 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

4. Initial Laboratory Evaluation

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

<table>
<thead>
<tr>
<th></th>
<th>Na+</th>
<th>K+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>132</td>
<td>3.8</td>
</tr>
<tr>
<td>3 PM</td>
<td>BUN 23, Cr. 1.2</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>1.2 mcg/dl</td>
<td></td>
</tr>
</tbody>
</table>

- ACTH Stimulation test:

<table>
<thead>
<tr>
<th></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 post ACTH</td>
<td>2.1/5</td>
<td></td>
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</table>

- Diagnosis: Central Adrenal Insufficiency

Presenter Disclosure Information

The following relationships exist related to this presentation:

- James V. Hennessey, MD, FACP, has no financial relationships to disclose.

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 Physiology

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 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

Addisonian Crisis

Clinical Features
- Hypotension
- Fever
- Dehydration
- GI distress:
  - Nausea / vomiting
  - Abdominal pain
- Weakness
- Apathy

Lab Abnormalities
- Hyponatremia,
- Hyperkalemia
- Hypoglycemia
- Lymphocytosis
- Eosinophilia

Precipitating Factors
- Physical stressors
  - Infections
  - Trauma

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
Adrenal Insufficiency
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

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

Adrenal Insufficiency
Treatment: Acute
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”
Pituitary Disorder Considerations

**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  

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 – >10 mm  

Pituitary Adenomas: Biology

- Derived from Rathke’s pouch (oral ectoderm)  
- Comprised of 5 cell types  
- Secretes 6+ neuropeptides  
- Controlled by Releasing Hormones from the hypothalamus & feedback from target organs  

Posterior Pituitary

- Neurohypophysis  
  - 20% of the gland  
  - Derived from Rathke’s pouch (oral ectoderm)  
  - Comprised of 5 cell types  
  - Secretes 6+ neuropeptides  
  - Controlled by Releasing Hormones from the hypothalamus & feedback from target organs

**Differential Diagnosis of Sellar/Parasellar Lesions**

**Benign Tumors**  
- Pituitary adenoma  
- Meningioma  
- Craniopharyngioma  
- Rathke’s cleft cyst  
- Epidermoid  
- Chordoma  
- Lipoma  
- Calculus cyst  
- Primitive Germ Cell Tumors  
  - Germinoma  
  - Teratoma  
  - Dysgerminoma  
  - Oligodendroglioma  
  - Ependymoma  
  - Astrocytoma  

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

**Metastatic Tumors**  
- Vascular Lesions  
- Hematologic Malignancies  
- Miscellaneous  
  - Empty sella syndrome  
  - Arachnoid cyst

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**Miscellaneous**

- Empty sella syndrome  
- Arachnoid cyst

**Pituitary Patient Evaluation**

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

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

- **Hyperfunction:**  
  - Hyperthyroidism  
  - Hypogonadism  
  - Prolactin excess  
  - Cushing’s 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)
  - TSH nl to low, FT4 low = Hypothyroidism
  - TSH nl to high, FT4 high C/W TSH secreting tumor

- **Reproductive**
  - Prolactin (with dilution if macroadenoma)
  - Elevation, consider differential diagnosis
  - > 100 likely prolactinoma
  - FSH, LH AND
  - Testosterone (men)
  - Estradiol (women)

**Critical to assess prolactin prior proceeding to surgery**

- **Adrenal**
  - ACTH AND Cortisol
  - ACTH nl to low, Cortisol low C/W Adrenal Insufficiency
  - Low dose ACTH stimulation
  - ACTH nl to high and Cortisol high C/W Cushing's
  - Dexamethasone suppression testing

**Extra tests required if GH or ACTH excess is suspected**

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**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>1.8</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, infiltrations, 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, risperidone, olanzapine
- Estrogens
- Antihistamines
- Cholinergic agonists
- Anesthetics
- Anticonvulsants
  - GI motility agents:
    - Cimetidine, metoclopramide

**Less Common**
- Antihypertensives
  - Methyldopa, reserpine, verapamil
- Antidepressants
  - Triyclics, SSRI's (minimal)
- Opiates
- Neuropeptides
- DA receptor agonists
- 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

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>1.3</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>

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!!

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

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 most important
  - 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 post operatively
- MRI typically repeated at 12 week visit to serve as new baseline
- Annual follow up recommended or as dictated by clinic status
  - Hormonal assessment
  - 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

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