Functional Pituitary Adenomas

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Outline

- Prolactinoma
- Acromegaly
- Cushing’s disease
- Thyrotroph adenomas
- Gonadotroph adenomas
Hyperprolactinemia

• Clinically apparent prolactinomas: 5-50/100,000

• Hypogonadism
  – Prolactin inhibits gonadotropin release
  – Full spectrum of severity
  – Leads to bone loss (trabecular)

• Galactorrhea
Causes of Hyperprolactinemia

- Physiology: pregnancy, lactation, chest wall stimulation, intercourse
- Medications: dopamine antagonists, estrogen, opiates, marijuana
- Pituitary: prolactinoma, non-prolactinoma pituitary disease
- Renal failure (PRL not cleared by dialysis)
- Primary hypothyroidism (elevated TRH; may be accompanied by pituitary hyperplasia)
Diagnosis of Prolactinomas

- Serum draw, any time of day
- Avoid chest wall stimulation, sexual intercourse, intense exercise for 24 hours prior
- Serial dilution of serum samples eliminates the “hook effect;” consider when a large adenoma is accompanied by a mildly elevated prolactin
- >500 mcg/L diagnostic for macroprolactinoma
- 250-500 mcg/L likely macroprolactinoma, but occasionally risperidone and metoclopramide can cause PRLs in the 200s
- 95-250 mcg/L: prolactinoma vs non-tumor causes
- <95 mcg/L: microprolactinoma, non-functioning adenoma, or non-tumor causes
  - Macroadenomas leading to stalk inhibition as the cause of hyperprolactinemia typically lead to PRLs < 95 mcg/L
Drug Induced Hyperprolactinemia

- Usually associated with PRL 25-100 mcg/L, occasionally into 200s with metoclopramide, risperidone, phenothiazines
- Prolactin should normalize within 3 days of holding the suspicious medication
- Obtain MRI if drug cannot be held or if onset of hyperprolactinemia does not coincide with therapy initiation
- 40-90% of patients on typical anti-psychotics will have hyperprolactinemia
- May be symptomatic (galactorrhea, hypogonadism, bone loss)
- If symptomatic, consider switch to alternative therapy or administration of replacement estrogen/testosterone
Prolactinomas: Treatment

- Dopamine agonists are mainstay of therapy
  - Cabergoline is first line
    - Side effects: headache, nausea, light-headedness
    - Normalization of prolactin in 80-99% of patients
    - Resolution of hypogonadism in majority of patients
    - Tumor shrinkage in 80-90% patients
  - Bromocriptine is second line
    - More of the same side effects
    - Cost is similar
    - Lower efficacy for outcomes
- Consider surgery for rapid visual loss
Microprolactinomas

- Rarely progress to macroprolactinomas
- Asymptomatic: no treatment necessary
- If symptomatic:
  - Females desiring pregnancy or males: cabergoline
  - Females not desiring pregnancy: cabergoline OR combined oral contraceptive
Acromegaly

- Rare: annual incidence of six per million people
- Mean age at diagnosis 40-45 years
  - If GH rises prior to epiphyseal growth plate fusion, then this leads to “pituitary gigantism”
- Vast majority of cases are due to excess GH secretion from a pituitary adenoma
- Insidious onset: in hindsight, symptoms begin on average 12 years prior to diagnosis
Acromegaly: Clinical Features

- Clinical features due to excess of both GH and IGF-1
- Overgrowth of many tissues: connective tissue, cartilage, bone, skin, visceral organs
- Cardiovascular disease and sleep apnea
- Metabolic disorders
- Colon neoplasia
Acromegaly: Clinical Features

- Soft tissue: hands, feet (ring/shoe size), tongue (macroglossia), nerve impingements (carpal tunnel), pharynx/larynx (sleep apnea in 50-70%)
- Bone: coarse facial features, enlarged jaw (macronathia), teeth spread apart, dental malocclusions, increase in BMD
- Skin: skin thickens (difficult venipuncture), skin tags, excessive sweating, hirsutism
- Joints: hypertrophic arthropathy
- Viscera: thyroid (goiter +/- nodules)
Acromegaly: Clinical Features

- Cardiovascular: HTN, LVH, diastolic dysfunction
- Metabolic: insulin resistance, DM2, hypertriglyceridemia
- Colon neoplasms: questionable increase in rates of colon cancer, but definite increase in colonic polyps as well as death from colon cancer
- Mortality: overall standard mortality ratio of 1.72, down to 1.09 following biochemical cure
When to Suspect Acromegaly

• Combination of DM2, sleep apnea, arthritis/tendonitis, especially if BMI is normal or in the absence of a FH of DM2
• New dental malocclusions
• Heat intolerance, sweating
• Hand/foot swelling
When to Suspect Acromegaly

• Combination of DM2, sleep apnea, arthritis/tendonitis, especially if BMI is normal or in the absence of a FH of DM2
• New dental malocclusions
• Heat intolerance, sweating
• Hand/foot swelling
75 yo white female with prior HTN, pre-DM, noted to have facial features of acromegaly
During a hospitalization for diverticulitis. IGF-1 760, GH 20, MRI showed 1.8cm sellar mass.
Underwent transphenoidal resection with residual disease post-operatively, in remission
Now on medical therapy (pegvisomant). 81 years young now and doing great!
Acromegaly: Diagnosis

• Biochemical diagnosis, not a clinical diagnosis
• Screening IGF-1
  – Nearly always elevated in patients with acromegaly
  – Few physiologic causes of high IGF-1: puberty and pregnancy
  – Many causes of low IGF-1: hypothyroidism, malnutrition, uncontrolled DM, liver/kidney failure, oral estrogen use
• Confirmation: 75g oral glucose tolerance. At 2 hours, GH < 1 ng/ml rules out acromegaly.
• Pituitary MRI for localization
Clinical Features of Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td><strong>Features that best discriminate Cushing’s syndrome; most do not have a high sensitivity</strong></td>
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<tr>
<td>Easy bruising</td>
<td>Dorso cervical fat pad (“buffalo hump”)</td>
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<td>Facial plethora</td>
<td>Facial fullness</td>
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<tr>
<td>Proximal myopathy (or proximal muscle weakness)</td>
<td>Obesity</td>
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<tr>
<td>Striae (especially if reddish purple and &gt; 1 cm wide)</td>
<td>Supraclavicular fullness</td>
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<td>In children, weight gain with decreasing growth velocity</td>
<td>Thin skin</td>
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**Cushing’s syndrome features in the general population that are common and/or less discriminatory**

- Depression
- Fatigue
- Weight gain
- Back pain
- Changes in appetite
- Decreased concentration
- Decreased libido
- Impaired memory (especially short term)
- Insomnia
- Irritability
- Menstrual abnormalities
- Acne
- Peripheral edema
- Hirsutism or female balding
- Poor skin healing
Conditions associated with hypercortisolism in the absence of Cushing’s syndrome

**Conditions**

Some clinical features of Cushing’s syndrome may be present
- Pregnancy
- Depression and other psychiatric conditions
- Alcohol dependence
- Glucocorticoid resistance
- Morbid obesity
- Poorly controlled diabetes mellitus

Unlikely to have any clinical features of Cushing’s syndrome
- Physical stress (hospitalization, surgery, pain)
- Malnutrition, anorexia nervosa
- Intense chronic exercise
- Hypothalamic amenorrhea
- CBG excess (increased serum but not urine cortisol)
Abdominal striae

Central fat deposition

- Thinning of hair
- Acne
- Red cheeks
- Buffalo hump
- Moon face
- Supraclavicular fat pad
- Increased body and facial hair
- Weight gain
- Purple striae
- Pendulous abdomen
- Ecchymosis resulting from easy bruising
- Thin extremities with muscle atrophy
- Thin skin and subcutaneous tissue
- Slow wound healing

Real World Cushing’s

• 34 yo female with 18 months of weight gain (30 lbs), fatigue, depression. Restricted to 1000 calories/day, worked with a physical trainer, developed proximal weakness noted by her trainer. Progressed to the point that she had to use her arms to pull herself up stairs.

• 46 yo female with hypothyroidism, stable on levothyroxine for years, with residual complaints of fatigue, difficulty losing weight.
  – 2-3 year period of worsening overall stamina, anxiety, further weight gain. 2013 normal UFC and elevated ONDST. Went home to Equador for a year.
  – 2015 further decline in health, mood, energy. UFC now elevated, salivary cortisols elevated and ONDST abnormal.
  – 2.8mm pituitary adenoma, underwent TSS with surgical cure
Real World Cushing’s

- 74 yo white female undergoes MRI for headaches, found to have a 1.2cm pituitary mass not seen in 2009. Stable HTN, new dx pre-DM.
- Definite truncal obesity, thin arms/legs noted on exam; notes “everyone in my family looks like this,” but then after further discussion does note that her body habitus has shifted significantly over the prior 12-18 mos. Some fatigue, decline in stamina.
- Abnormal ONDST, underwent TSS 12/17 with path confirming an ACTH producing adenoma.
When to Consider Cushing’s Syndrome

• Rapid weight gain with proximal weakness
• Patients with unusual features for age (HTN, osteoporosis)
• Patients with multiple and progressive features
• Adrenal adenomas
Diagnosis of Cushing’s Syndrome

- 24h urine free cortisol (UFC)- 2 samples
- Late night salivary cortisols- 2 samples
- 1mg overnight dexamethasone suppression test (ON DST)

Do not use:
- 8 am cortisol
- Imaging prior to biochemical diagnosis
Diagnosis of Cushing’s Syndrome

- For all: rule out any exogenous glucocorticoid use (oral, injected, inhaled, topical)
- 24 hour UFC
  - May miss mild cases
  - Avoid if CrCl < 60ml/min (falsely low values)
- Salivary cortisol
  - 1-2 hours after normal bedtime; do not use if pt does not have regular sleep/wake cycle
- 1mg ONDST
  - Avoid with seizure meds, oral estrogen
Diagnosis of Cushing’s Syndrome

• Start with 1 or 2 tests, depending on pre-test probability based on history/exam
• If all tests are negative, Cushing’s Syndrome is less likely but not impossible
• If symptoms progress in the next months-years, then re-evaluation is warranted
Take Home Points

- Prolactinomas are very common
  - All pituitary adenomas, cases of amenorrhea/oligomenorrhea deserve a PRL screen
  - Many causes of hyperprolactinemia other than prolactinomas
- Cushing’s syndrome and acromegaly much less common, but probably under-diagnosed
  - Consider Cushing’s for rapidly progressive symptoms
  - Even if initial Cushing's tests are normal or equivocal, ask patients to follow up if symptoms progress
References

- 2008 J Clin Endocrinol Metab 93(5):1526. The Diagnosis of Cushing’s Syndrome: An Endocrine Society Clinical Practice Guideline
- 2011 J Clin Endocrinol Metab 96(2): 273. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline
- www.endotext.org