Functional Pituitary Adenomas

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Jo-Jo

CC: 6 yo male dog, fatigued
HPI: Progressive fatigue, lack of motivation, weight gain around midsection with weakening hind legs
Diagnosis: Cushing’s Disease!
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
  – 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 insufficiency (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
- Females desiring pregnancy: 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
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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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| **Features that best discriminate Cushing’s syndrome; most do not have a high sensitivity** | Easy bruising  
   Facial plethora  
   Proximal myopathy (or proximal muscle weakness)  
   Striae (especially if reddish purple and > 1 cm wide)  
   In children, weight gain with decreasing growth velocity |
| **Cushing’s syndrome features in the general population that are common and/or less discriminatory** | Dorosocervical fat pad (“buffalo hump”)  
   Facial fullness  
   Obesity  
   Supraclavicular fullness  
   Thin skin  
   Peripheral edema  
   Acne  
   Hirsutism or female balding  
   Poor skin healing |
| Depression  
   Fatigue  
   Weight gain  
   Back pain  
   Changes in appetite  
   Decreased concentration  
   Decreased libido  
   Impaired memory (especially short term)  
   Insomnia  
   Irritability  
   Menstrual abnormalities |
Conditions associated with hypercortisolism in the absence of Cushing’s syndrome

<table>
<thead>
<tr>
<th>Conditions</th>
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<tbody>
<tr>
<td>Some clinical features of Cushing’s syndrome may be present</td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Depression and other psychiatric conditions</td>
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<tr>
<td>Alcohol dependence</td>
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<tr>
<td>Glucocorticoid resistance</td>
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<tr>
<td>Morbid obesity</td>
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<tr>
<td>Poorly controlled diabetes mellitus</td>
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<tr>
<td>Unlikely to have any clinical features of Cushing’s syndrome</td>
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<tr>
<td>Physical stress (hospitalization, surgery, pain)</td>
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<td>Malnutrition, anorexia nervosa</td>
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<td>Intense chronic exercise</td>
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<td>Hypothalamic amenorrhea</td>
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<td>CBG excess (increased serum but not urine cortisol)</td>
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July 2009, with Cushing’s Disease again
Rapidly progressing symptoms: think Cushing’s syndrome!
When to Consider Cushing’s Syndrome

- Rapid weight gain
- 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 (ONDST)

- 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 unlikely
• 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
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