Functional Pituitary Adenomas

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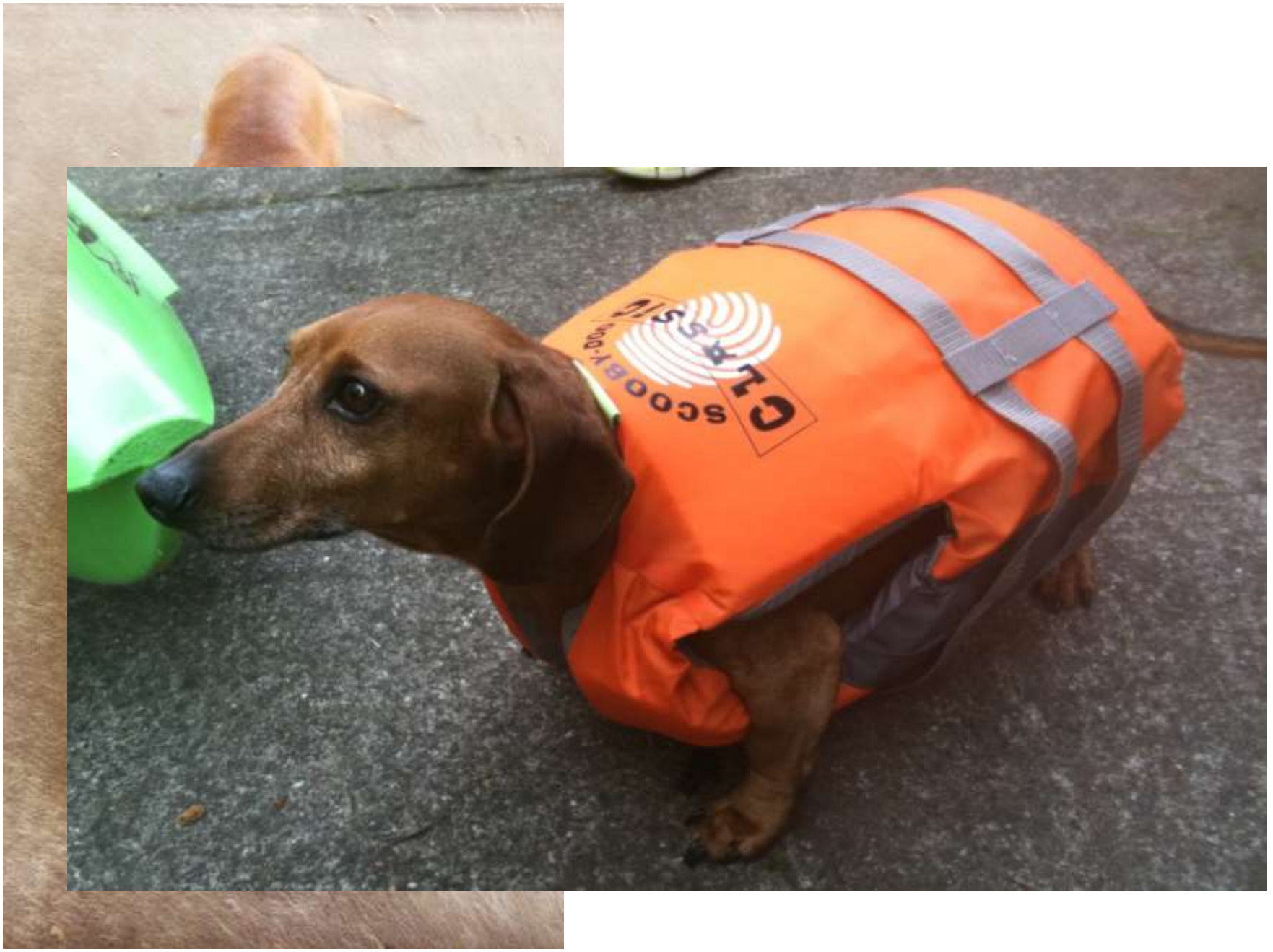
Jo-Jo

CC: 6 yo male dog, fatigued

HPI: Progressive fatigue, lack of motivation, weight gain around midsection with weakening hind legs

Diagnosis: Cushing's Disease!


SCOOBY-DOO
CLASSIC

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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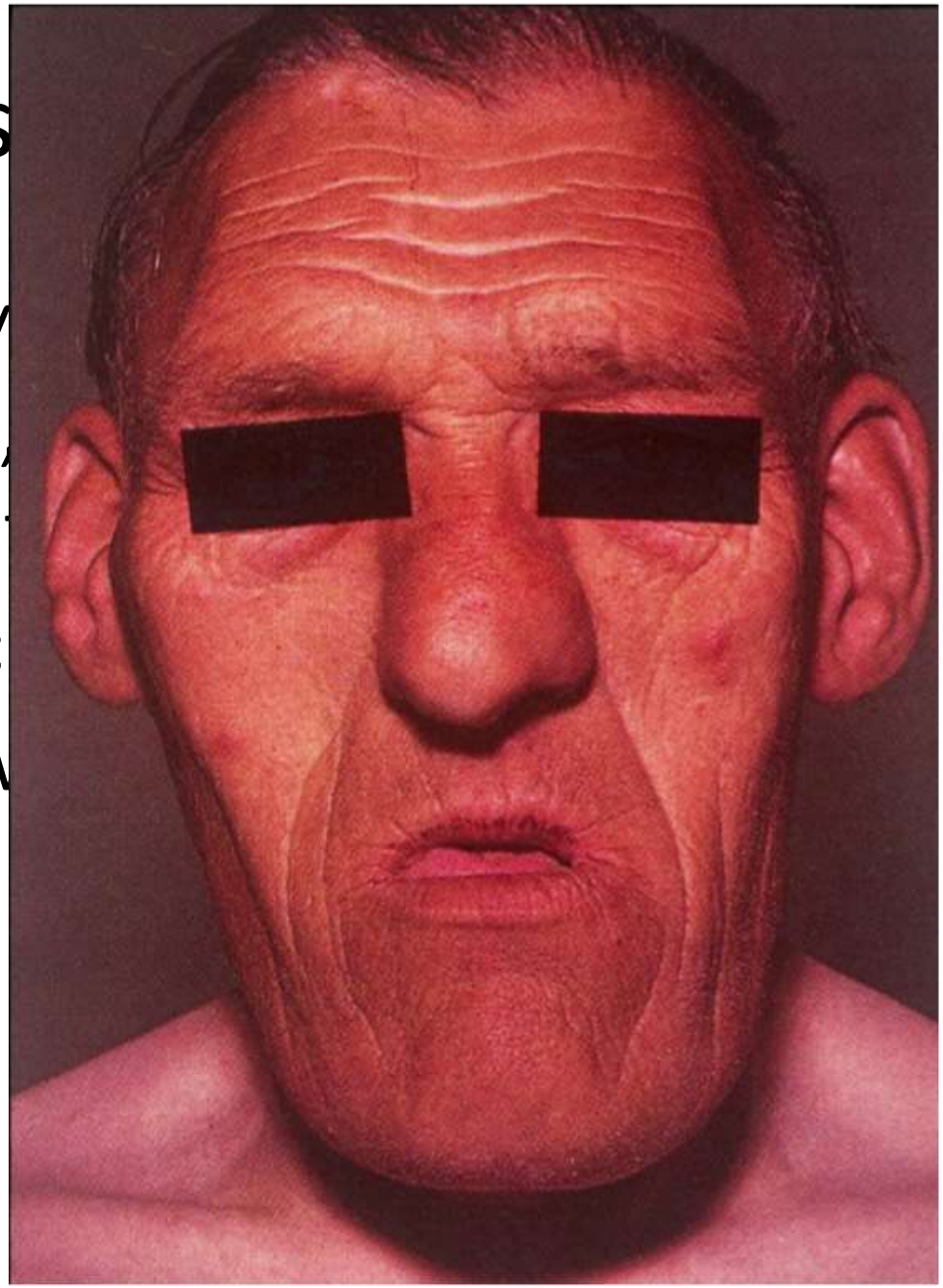
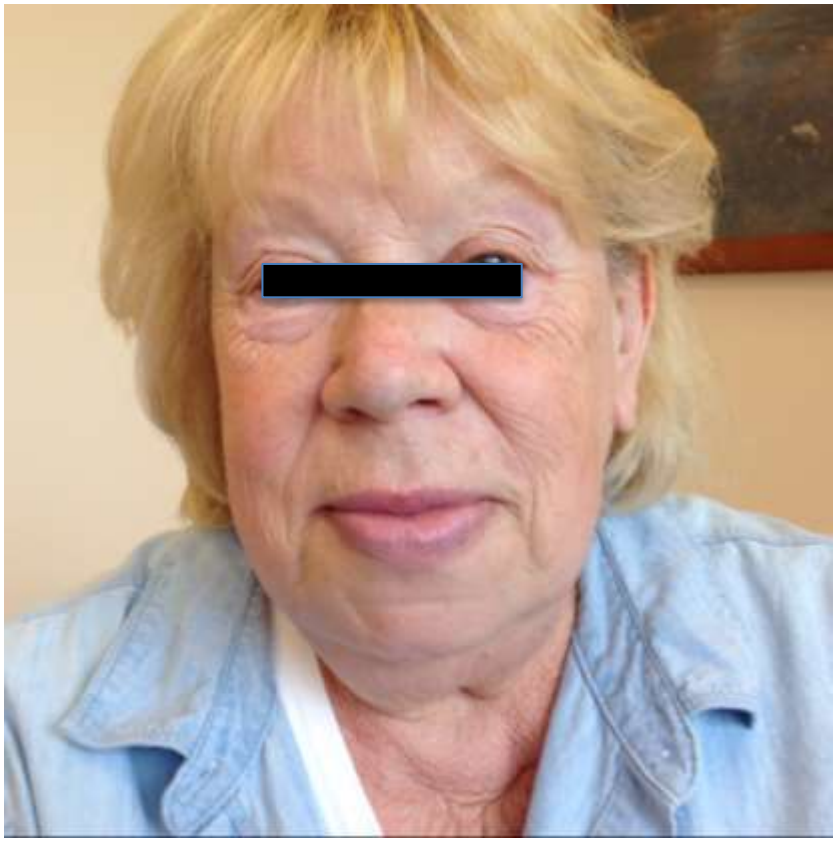
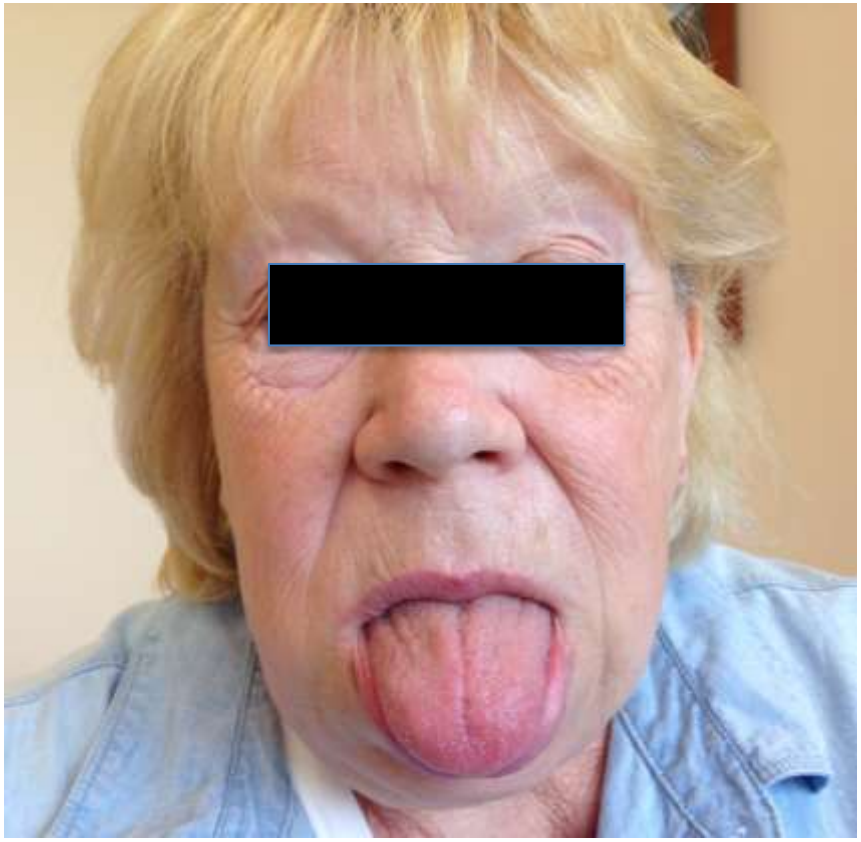






Acromegaly: Diagnosis

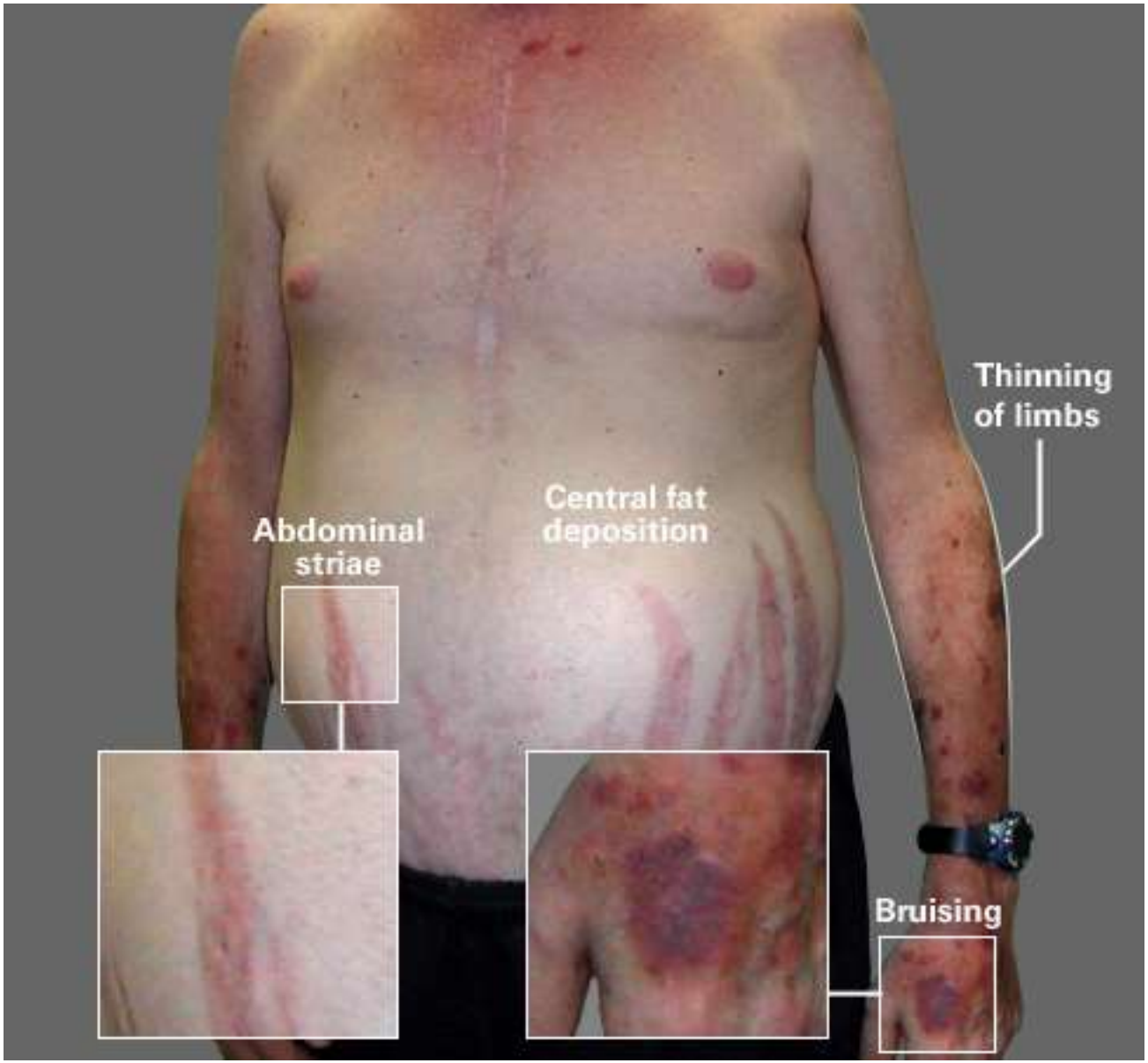
- Biochemical diagnosis, not a clinical diagnosis
- Screening IGF-1
  - Nearly always elevated in patients with acromegaly
  - Few physiologic causes of high IGF-1: puberty and pregnancy
  - Many causes of low IGF-1: hypothyroidism, malnutrition, uncontrolled DM, liver/kidney failure, oral estrogen use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

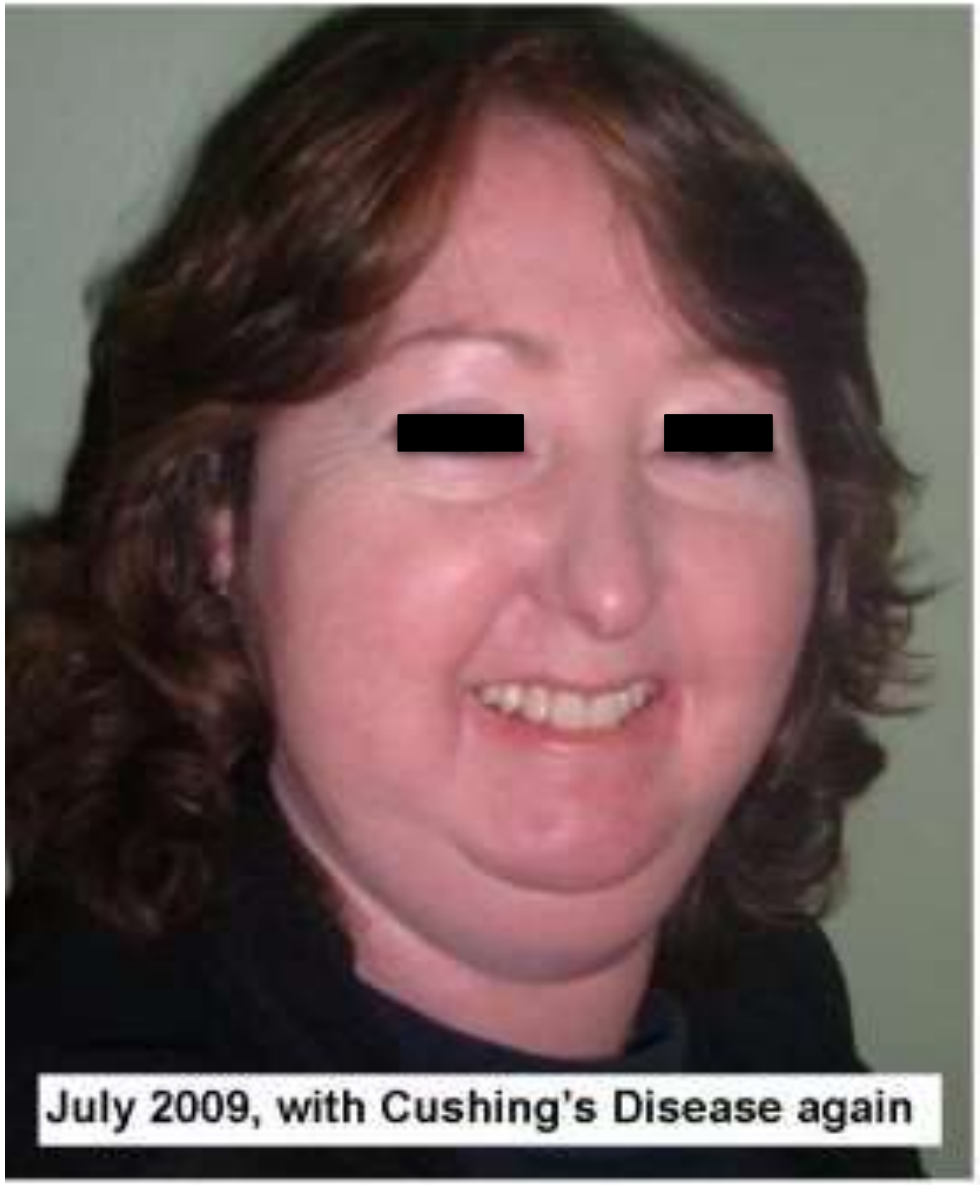
Clinical Features of Cushing's Syndrome

Symptoms	Signs
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	
Depression	Dorsocervical fat pad ("buffalo hump")
Fatigue	Facial fullness
Weight gain	Obesity
Back pain	Supraclavicular fullness
Changes in appetite	Thin skin[b]
Decreased concentration	Peripheral edema
Decreased libido	Acne
Impaired memory (especially short term)	Hirsutism or female balding
Insomnia	Poor skin healing
Irritability	
Menstrual abnormalities	

Conditions associated with hypercortisolism in the absence of Cushing's syndrome[a]

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)


Thinning of limbs
Central fat deposition
Abdominal striae
Bruising


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
- 2014 J Clin Endocrinol Metab 99(11): 3933. Acromegaly: An Endocrine Society Clinical Practice Guideline
- www.endotext.org