

Pituitary Disorders

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 - Clinical focus: Neuroendocrinology and Endocrine Genetics
 - Research focus: GnRH regulation, Pituitary adenomas



DISCLOSURES

Nothing to disclose.



OBJECTIVES

Lecture is a general neuroendocrine review.

Goal is to discuss:

- Neuroendocrine physiology
- Diagnostic approach and management of pituitary disorders



Outline

- I. Pituitary Physiology
- II. Causes of Pituitary Disease
- III. Approach to Evaluation and Management of Pituitary Disease
 - A. Pituitary Hormone Excess
 - B. Pituitary Hormone Deficiency
 - C. Mass Effects



Pituitary Gland

Anterior Pituitary

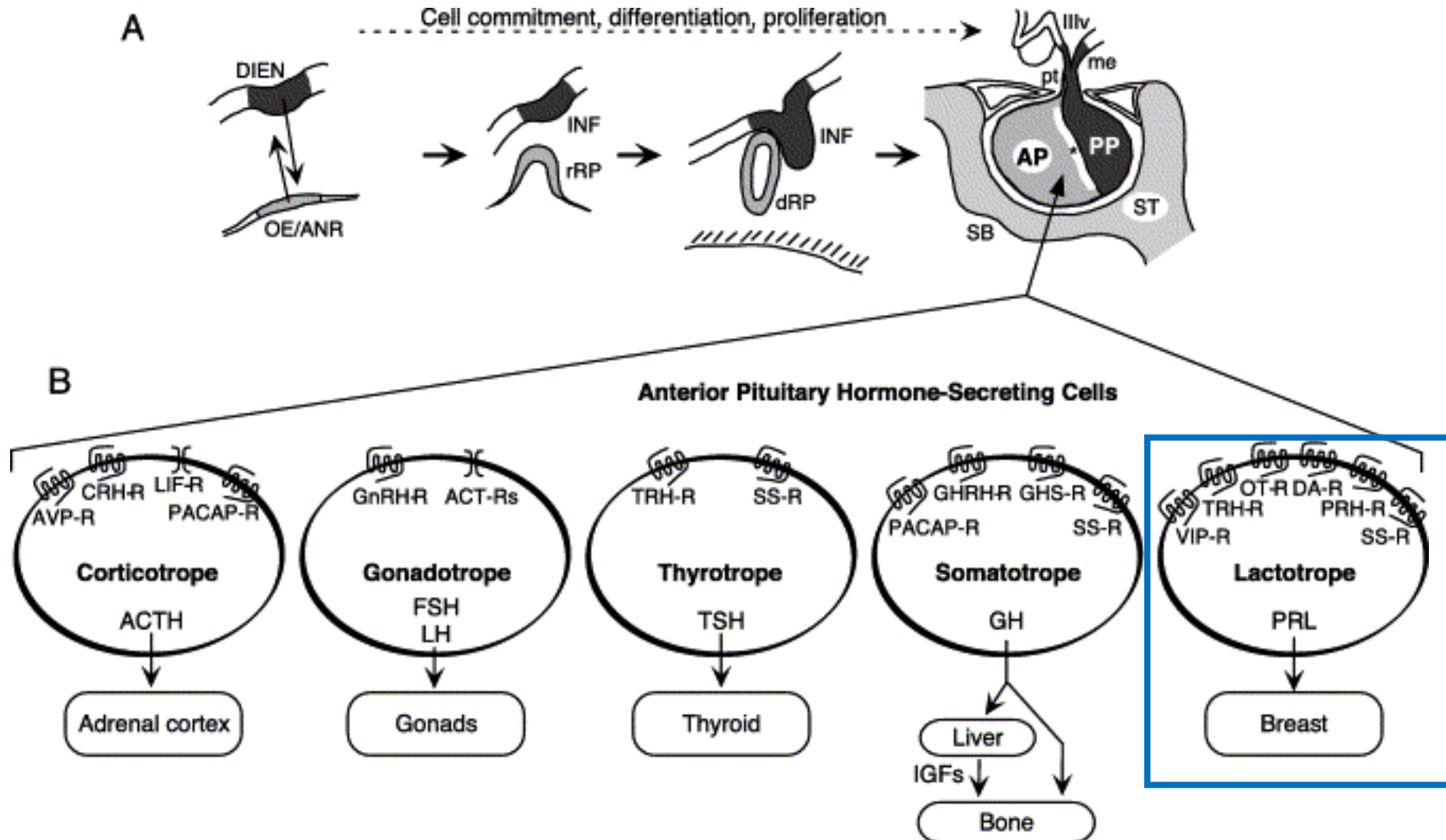
- Adenohypophysis
- 80% of the gland
- Derived from Rathke's pouch (oral ectoderm)
- Comprised of 5 cell types
- Secretes 6 hormones
- Controlled by neuropeptides from the hypothalamus & feedback from target organs

Posterior Pituitary

- Neurohypophysis
- 20% of the gland
- Direct extension of the hypothalamus
- Axon terminals from SON and PVN of hypothalamic neurons
- Hormone produced in hypothalamus, stored in pituitary

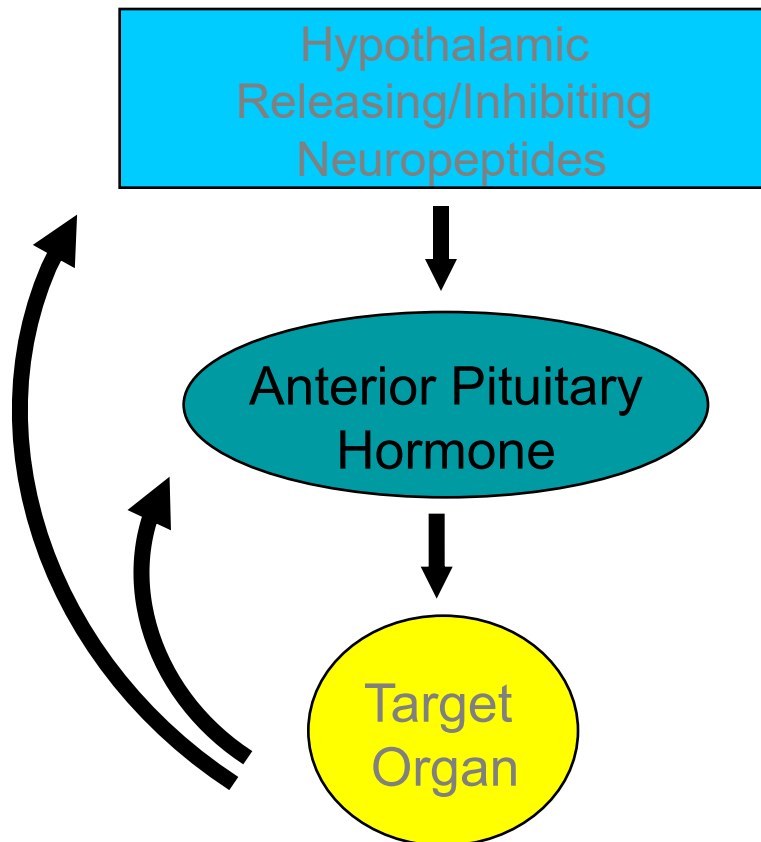


Pituitary Embryogenesis

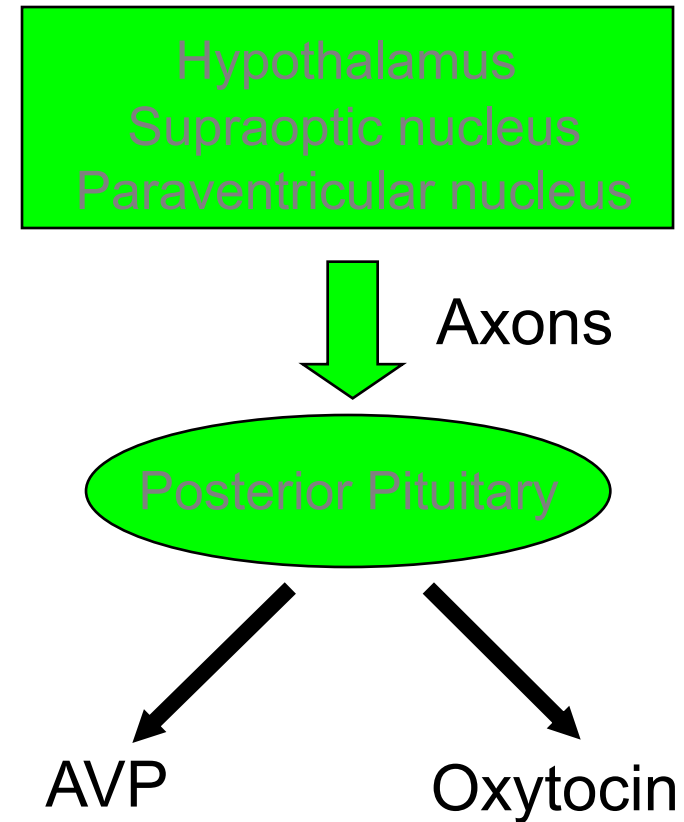


Pituitary Physiology

Anterior Pituitary



Posterior Pituitary



Approach to Pituitary Disorders

Evaluate:

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

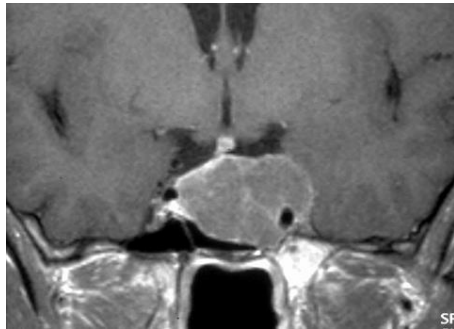


Clinical Case 1

- ❑ 69 year-old female presented for evaluation of headaches
- ❑ ROS + fatigue, depression, and cold intolerance.
- ❑ MRI scan revealed 2 x 3.2 cm sellar mass, extending suprasellarly to the optic chiasm and into the L cavernous sinus



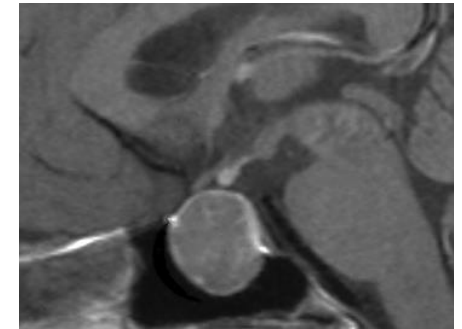
Normal



Adenoma



Normal



Adenoma

=> Let's talk about sellar lesions

Differential Diagnosis of Sellar/Parasellar Lesions

Benign Tumors

Pituitary adenoma (carcinoma)

Meningioma

Cell Rest Tumors

Craniopharyngioma

Rathke's cleft cyst

Epidermoid

Chordoma

Lipoma

Colloid cyst

Primitive Germ Cell Tumors

Germinoma

Teratoma

Dysgerminoma

Oligodendroglioma

Ependymoma

Astrocytoma

Granulomatous, Infectious, and Inflammatory

Lymphocytic hypophysitis

Abscess

Sarcoidosis

Tuberculosis

Eosinophilic granulomatosis

Mycoses

Metastatic Tumors

Vascular Lesions

Hematologic Malignancies

Miscellaneous

Empty sella syndrome

Arachnoid cyst



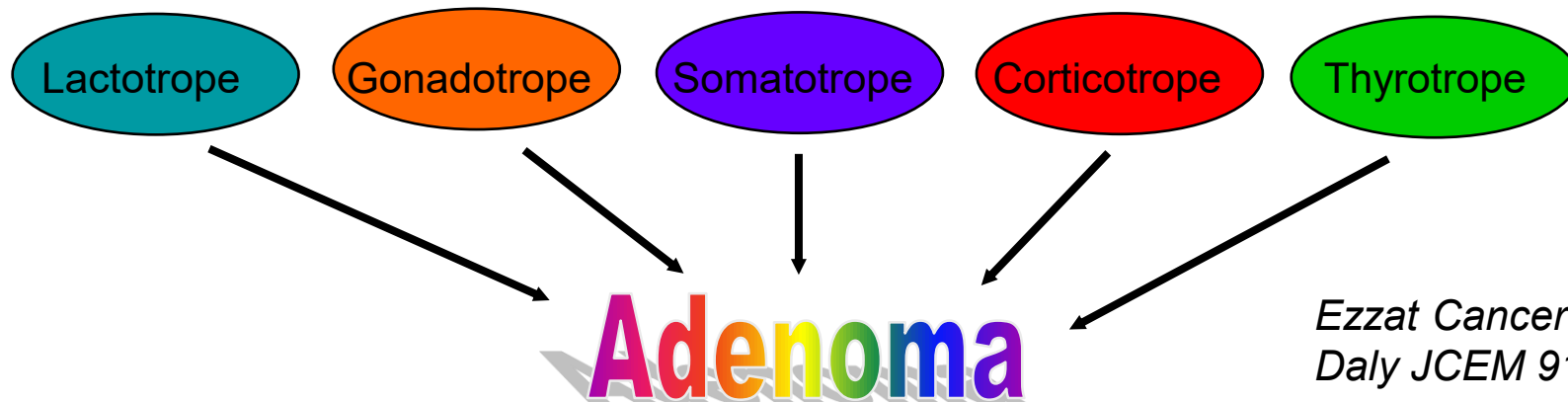
Pituitary Adenomas: Epidemiology

Pituitary adenomas account for 10-15% of all intracranial tumors.

- MRI studies 14.4%
- Autopsy series 12-22.5%

Classified according to size.

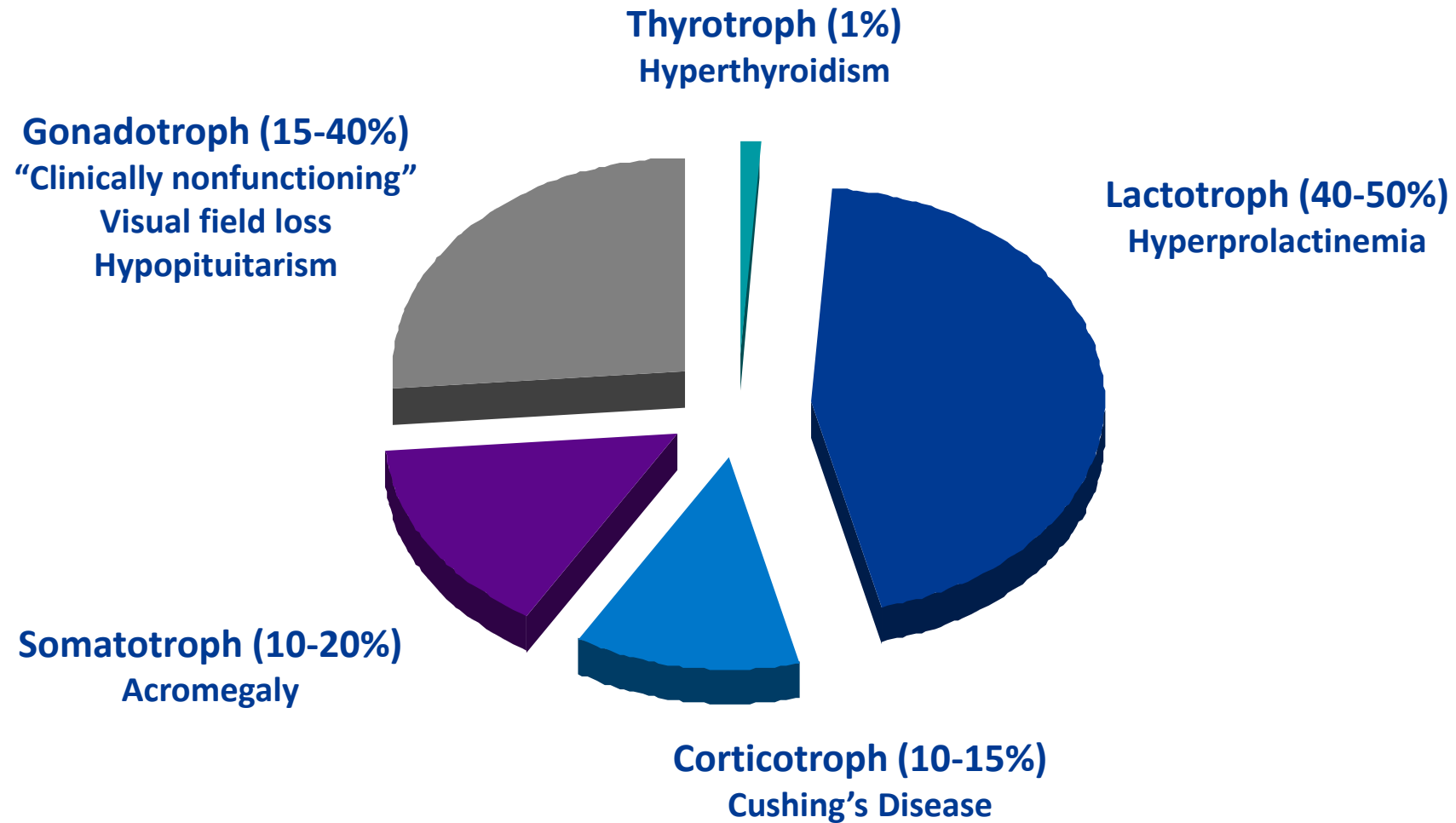
- Microadenomas < 10 mm
- Macroadenomas > 10 mm



Ezzat Cancer 101: 613, 2004
Daly JCEM 91: 4769, 2006



Pituitary Adenoma Types



Patient Evaluation

- History:

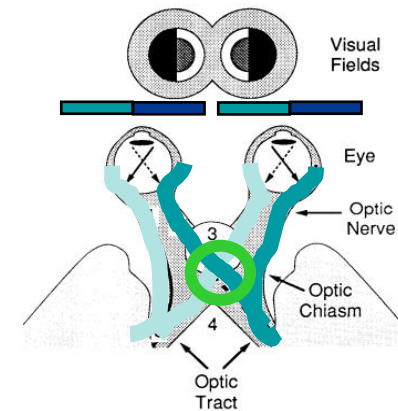
Questions regarding endocrine hypo- or hyper-function.
Think of anterior & posterior pituitary.

- Hyperfunction:

Cushing's syndrome
Hyperthyroidism
GH excess
Prolactin excess

- Hypofunction:

Adrenal insufficiency
Hypothyroidism
GH deficiency
Hypogonadism
Diabetes insipidus/Arginine vasopressin deficiency



- Neurological “mass effect” symptoms: headache, visual disturbance.



Standard Pituitary Laboratory Tests

- Thyroid
 - TSH, free T4
- Reproductive
 - Prolactin
 - FSH, LH, testosterone (men) or estradiol (women)
- Growth Hormone
 - IGF-1
- Adrenal
 - Cortisol
 - ACTH

Critical to assess prolactin prior
proceeding to surgery

Extra tests may be required if GH or
ACTH excess is suspected



Clinical Case 1-2

Labs

- ❑ IGF-1 83 ng/mL (-2SD)
- ❑ AM Cortisol 3.2 ug/dL
- ❑ FSH 6 IU/L
- ❑ FT4 1.0 ng/dL, TSH 1.5
- ❑ Prolactin 33 ng/ml (nl < 23)

What is the diagnosis?

What are the treatment options?



“Nonfunctioning” Adenomas

- Appear clinically inactive.
 - Often secrete α -subunit, FSH β or LH β subunit or sometimes intact gonadotropins.
- One third of all pituitary tumors.
- Often present with mass effect symptoms only and no evidence of hormonal overactivity.
- Some patients with large tumors present with pituitary hormonal deficiencies.
- Treatment of choice is surgery. Observation is an option



Clinical Case 2-1

27-year-old woman, G1P1, menses never resumed after d/c OCP's.
Denies headaches, visual or another neuro c/o. Can't seem to lose weight she gained with pregnancy. + galactorrhea x 6 mos.

Meds: none.

Physical Exam:

Intact visual field on confrontation.

Bilateral galactorrhea.

What should you look for on exam?
What is the differential diagnosis?



Clinical Case 2-2

Labs

- ❑ Prolactin 283 ng/ml (nl < 23)
- ❑ HCG negative
- ❑ E2 11, LH 6 IU/L, FSH 5 IU/L
- ❑ IGF-1 183 ng/mL (nl)
- ❑ Cortisol 8.2 ug/dL
- ❑ FT4 1.0 ng/dL, TSH 1.5 uIU/mL

How do you interpret the lab values in association with the clinical presentation?

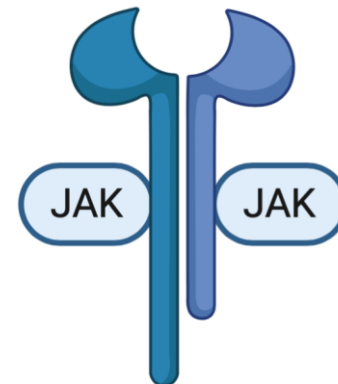
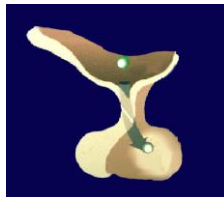
What is the next step?

What is the diagnosis?



Prolactin Physiology

- Produced by pituitary lactotrophs
- Tonic inhibition by hypothalamic dopamine
- Act at the prolactin receptor (type I cytokine receptor family)
- Primary physiological effect is induction of lactation



Cytokine receptors

Prolactin
Growth hormone

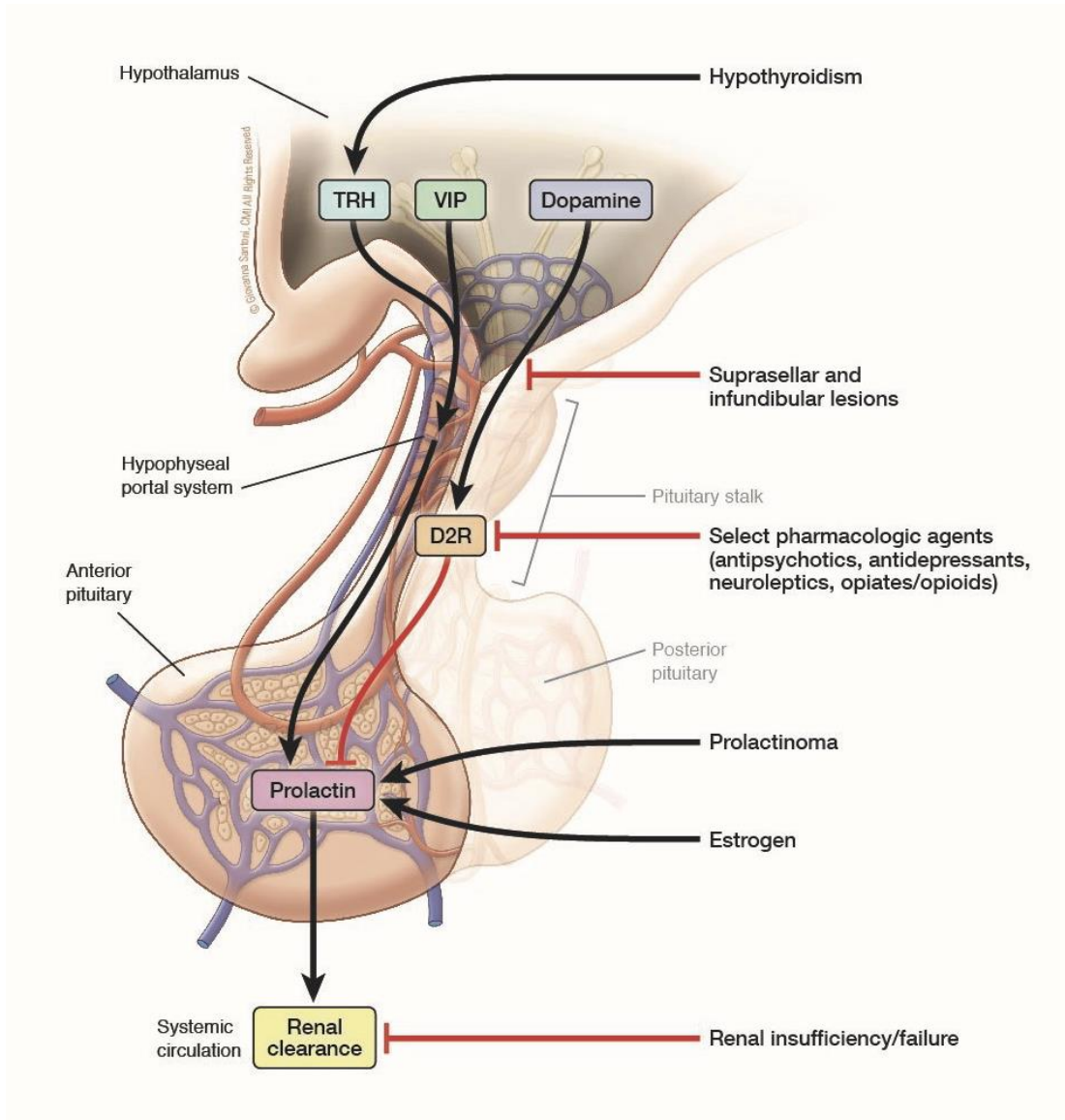
Clinical Presentation of Hyperprolactinemia

- **Galactorrhea ****
- **Hypogonadism ****
 - Oligo/amenorrhea
 - Infertility
 - Erectile dysfunction
 - Growth arrest / delayed puberty
- Mass effects if **tumor** is large





Pathophysiology of Hyperprolactinemia



Inhibition of dopamine or its receptor increases prolactin:

Suprasellar and infundibular lesions inhibit dopamine

Medications that block dopamine receptor

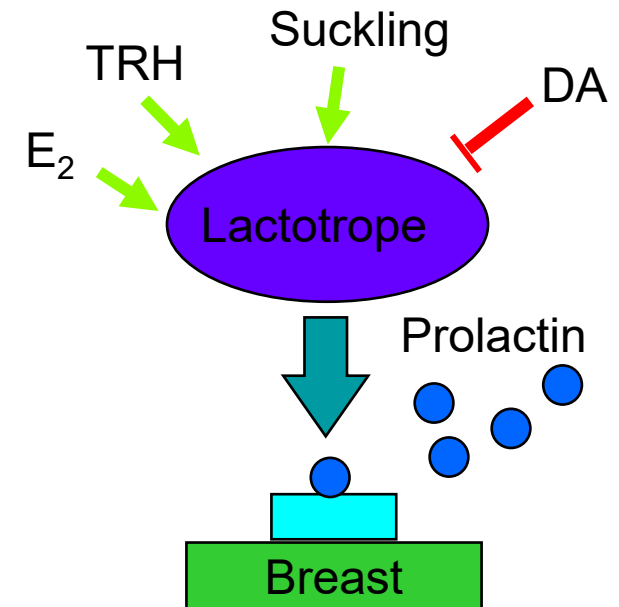
TRH and VIP & estrogen stimulate prolactin

Prolactin is cleared by the kidney

Decreased renal clearance increases serum prolactin levels

DDx: Hyperprolactinemia

- **Physiologic states:**
 - Pregnancy, Lactation, Exercise, Stress, Sleep
- **Medications**
- **Longstanding primary hypothyroidism**
- **Systemic disorders:**
 - Neurogenic chest wall lesion, renal failure, cirrhosis, seizures
- **Hypothalamic-pituitary stalk damage:**
 - Radiation, infiltrations, cysts, tumors, trauma
- **Prolactinoma**
- **Idiopathic**
- **Macroprolactinemia**





Medications causing prolactin excess

- ❑ Psychotropic
- ❑ Metoclopramide
- ❑ Antihypertensive (verapamil, α methyldopa)
- ❑ Opiates
- ❑ Cocaine
- ❑ Protease inhibitors
- ❑ Estrogens





Imaging – When Should You Do an MRI?

- ❑ Assess for physiologic, pharmacologic, and other pathophysiologic causes
 - ❑ Pregnancy test
 - ❑ TSH
 - ❑ BUN, creatinine

When a symptomatic elevated serum prolactin level is not associated with a clear secondary cause, a pituitary MRI scan should be performed to evaluate for the presence of a prolactinoma or other lesion (stalk effect), and to distinguish micro- from macroprolactinomas.



Prolactinomas: Treatment Options

General Treatment Options:

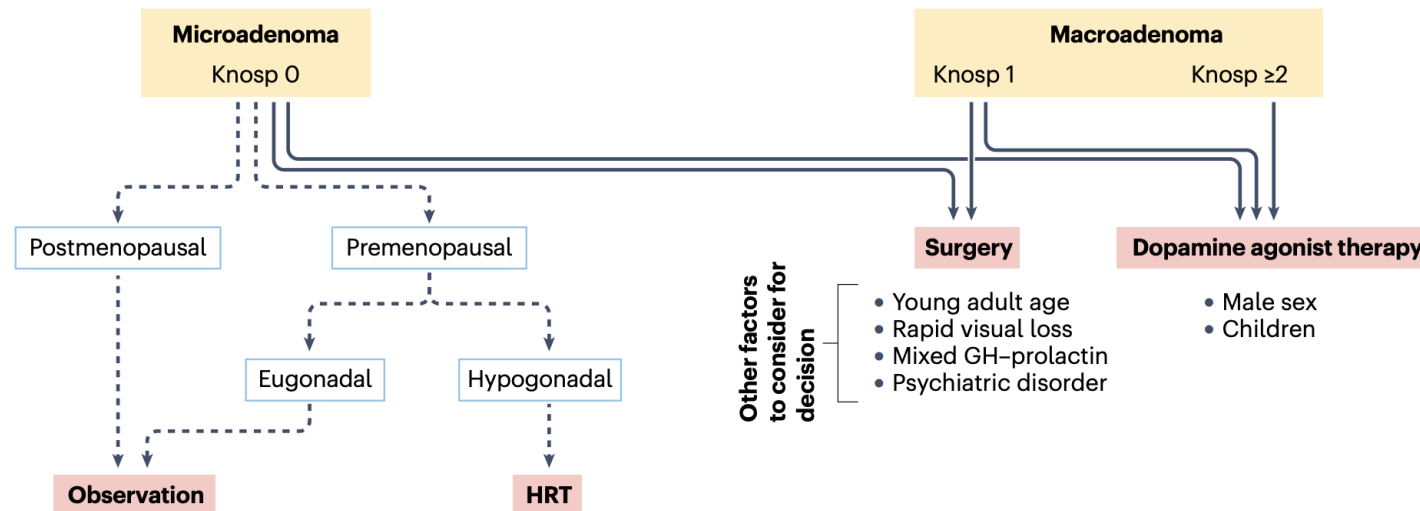
Medical therapy with dopamine agonists

- Cabergoline (preferred), bromocriptine

Transsphenoidal resection

- Second line therapy in most cases
- Microprolactinomas and well-encased macroprolactinomas (Knosp grade 0 and 1), the curative potential and risks of surgery should be discussed with patients in a multidisciplinary setting prior to medical treatment initiation

a Selecting a first-line treatment



Clinical Case 3-1

57-year-old male with multiple medical problems who recently presented to PCP with SOB, and CP. Found to have new onset CHF, hypoxia.

PMH: Arthritis, gout, nephrolithiasis, colon polyps, carpal tunnel syndrome, COPD.

Meds: Captopril, allopurinol, ASA, prednisone 5 mg/d, methotrexate.



Clinical Case 3-2

PE: 146/88 P82 BMI 30

HEENT: PERRLA, EOMI, VF full. Large tongue. Upper/lower dentures.

Neck: moderate symmetrical thyromegaly, no nodules palpated.

Lungs and CVD: bibasilar rales, RRR +S3

Abd: obese.

Ext: Large doughy hands. Shoe size 13, wide. No active joint inflammation.

Multiple skin tags.

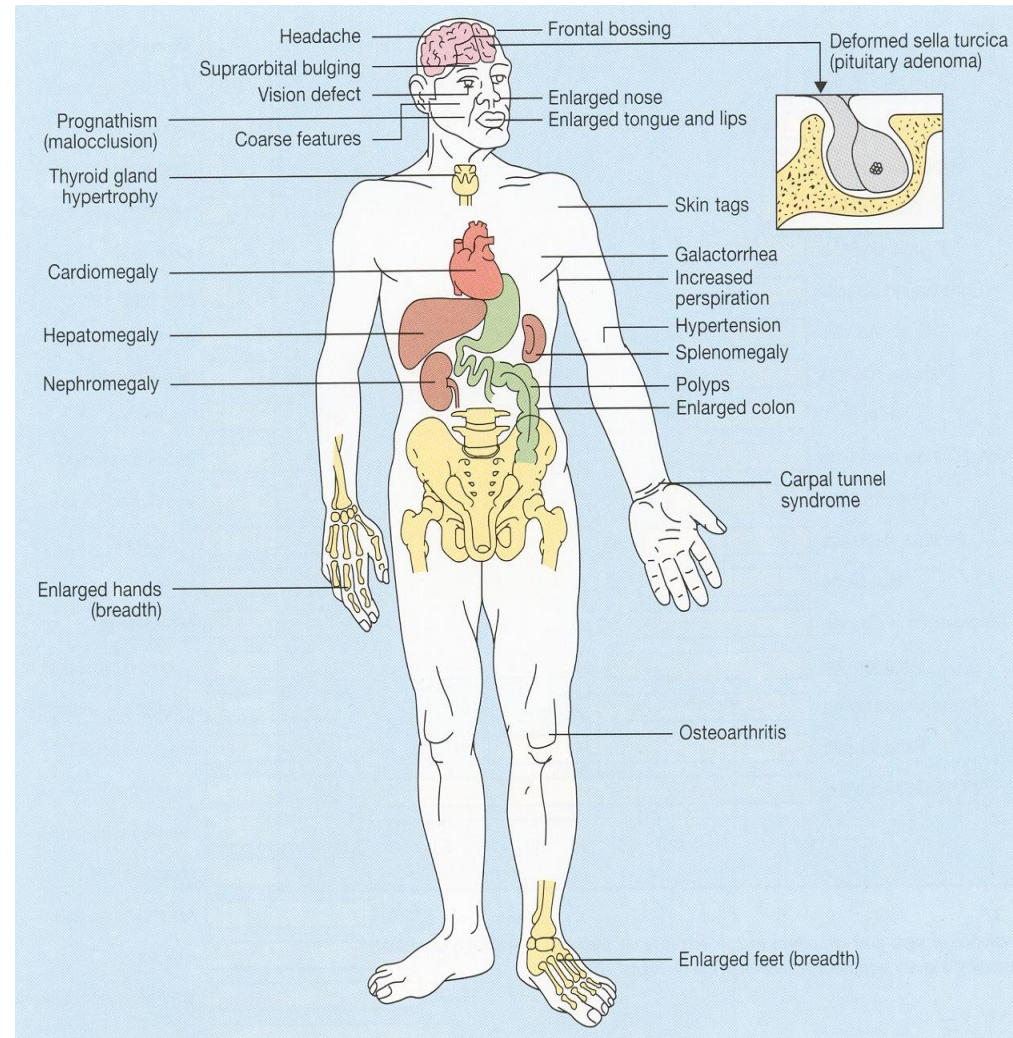
What diagnosis are you considering?

What lab tests would you like?



Clinical Features of Growth Hormone Excess

- ❑ Acral enlargement and/or coarse features
- ❑ Sweating
- ❑ Menstrual disorder
- ❑ Headaches
- ❑ Arthritis / carpal tunnel syndrome
- ❑ Diabetes or pre-diabetes
- ❑ Soft tissue hypertrophy
- ❑ Impotence or decreased libido
- ❑ Hypertension
- ❑ Visual field defects
- ❑ Obstructive sleep apnea
- ❑ Galactorrhea
- ❑ Coronary artery disease



Clinical Case 3-3

Labs:

IGF-1 985 ng/mL (high)

FT4 = 0.7 ng/dL (normal 0.7-2.7)

TSH 0.4 uIU/mL (normal 0.5-4.5)

FSH 11 IU/L

LH 7.4 IU/L

Testosterone 234 ng/dL (low normal)

Prolactin 7 ng/ml (normal)

What diagnosis are you considering now?

Would you order any radiologic tests at this time?



Acromegaly – diagnosis

❑ IGF-1

- ❑ Simple screening test
- ❑ Reference range: Matched by age / gender

❑ Growth hormone suppression test

- ❑ Only if diagnosis is questionable after measuring IGF1 levels
- ❑ OGTT with GH levels – should suppress $<0.4 \mu\text{g/L}$
 - ❑ 75g of glucose
 - ❑ GH + glucose levels every 30 minutes x 2 hours

❑ MRI

Early diagnosis of acromegaly equates to decreased morbidity and mortality and improved quality of life



Acromegaly: Treatment

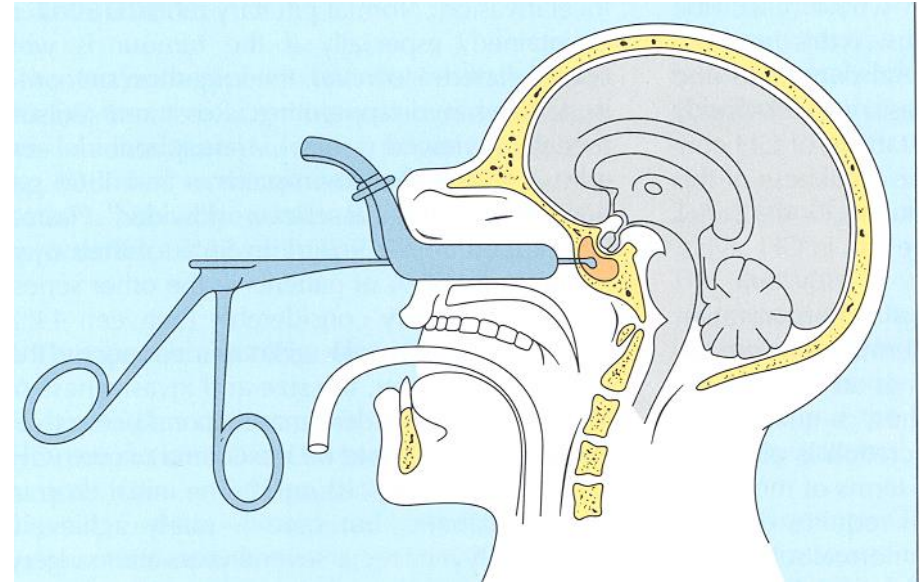
Surgery

Medical Therapy

- Somatostatin analogs
 - Octreotide LAR
 - Lanreotide
 - Pasireotide
- Cabergoline
- Pegvisomant

Radiation

- Conventional
- Radiosurgery



Goal is “biochemical cure”:
Normal IGF-1
Normal GH suppression



Pituitary Adenomas: Therapeutic Considerations

Treat symptoms related to mass effects.

- Restore or preserve vision
- Neurologic improvements – cranial nerves, headaches

Correct pituitary hyperfunction.

- Aim for biochemical cure

Medical hormone replacement for hypopituitarism.



Hypopituitarism - Management

Treatment based on correcting hormone deficiencies.

- *Adrenal* – hydrocortisone or prednisone. Use lowest dose possible.
 - May need stimulation testing for diagnosis
 - Stress dose coverage
 - Mineralocorticoid replacement not necessary.
- *Thyroid* – levothyroxine, after adrenal replacement
 - **remember TSH cannot guide Rx.
- *Gonadal* – Men require testosterone, women may require estrogen-progesterone replacement. Gonadotropins for fertility.
- *Growth hormone* – Need stimulation testing. Can treat with rhGH.
- *Prolactin* – no replacement available or required.
- *Posterior pituitary* – desmopressin (DDAVP)



MOC REFLECTIVE STATEMENT

“Take Home” Messages:

❖ When evaluating patients with pituitary disorders, let pituitary physiology be your guide. Evaluate:

- Pituitary hyperfunction
 - GH (acromegaly)
 - ACTH (Cushing’s disease – hypercortisolism)
 - Prolactin (galactorrhea, menstrual disorders, erectile dysfunction)
 - TSH (hyperthyroidism)
- Pituitary hypofunction – all hormone systems
- Mass effects (headache, visual dysfunction)

❖ Treatment is aimed at restoring normal pituitary function and can include: surgery, hormone replacement, medications



Question 1:

A patient presents with increasing ring and shoe size and changes in appearance as noted by her family. You suspect that she may have acromegaly. Which of the following tests is most helpful in establishing the diagnosis?

- A. Pituitary MRI scan
- B. Insulin tolerance test with GH levels
- C. Serum IGFBP3
- D. IGF-1 levels

D. Simple screening test. Reference range: Matched by age / gender



Question 2:

A 32 year old woman presents complaining of a 6 month history of irregular periods. Instead of her usual cycle of 28-30 days, her periods have been 6-8 weeks apart. Further questioning reveals that she has also noted a bit of milky fluid on her nipples on several occasions over the past few months. A serum prolactin level is 95 ng/mL (normal 2-16). Which of the following is not likely to cause hyperprolactinemia?

- A. A nonfunctioning pituitary macroadenoma.
- B. A prolactin-secreting microadenoma.
- C. Therapy with L-dopa for Parkinson's disease.
- D. Therapy with antipsychotic medication such as risperidone.
- E. Primary hypothyroidism.

C. L-Dopa crosses the blood brain barrier and is converted to dopamine in the central nervous system, used to treat Parkinson's disease. Dopamine inhibits prolactin secretion and can be used as a treatment for hyperprolactinemia.



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