# Disorders of the Hypothalamus and Pituitary

Presented by Deepika Panday , PGY5 Endocrine fellow

CME SEMINARS

# Disorders of the Hypothalamus and Pituitary

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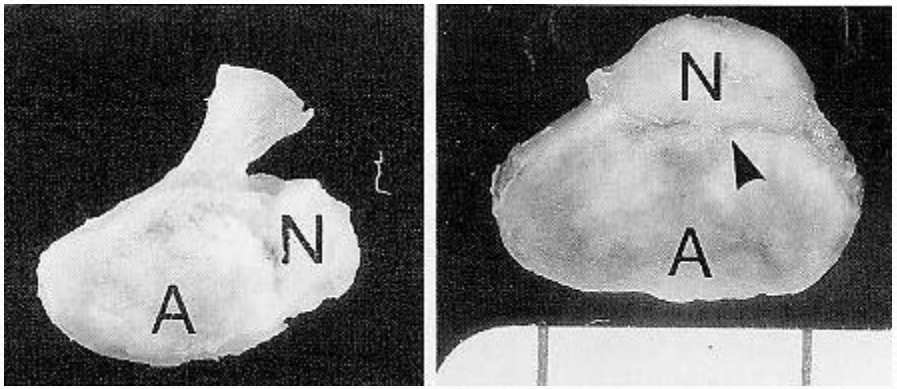
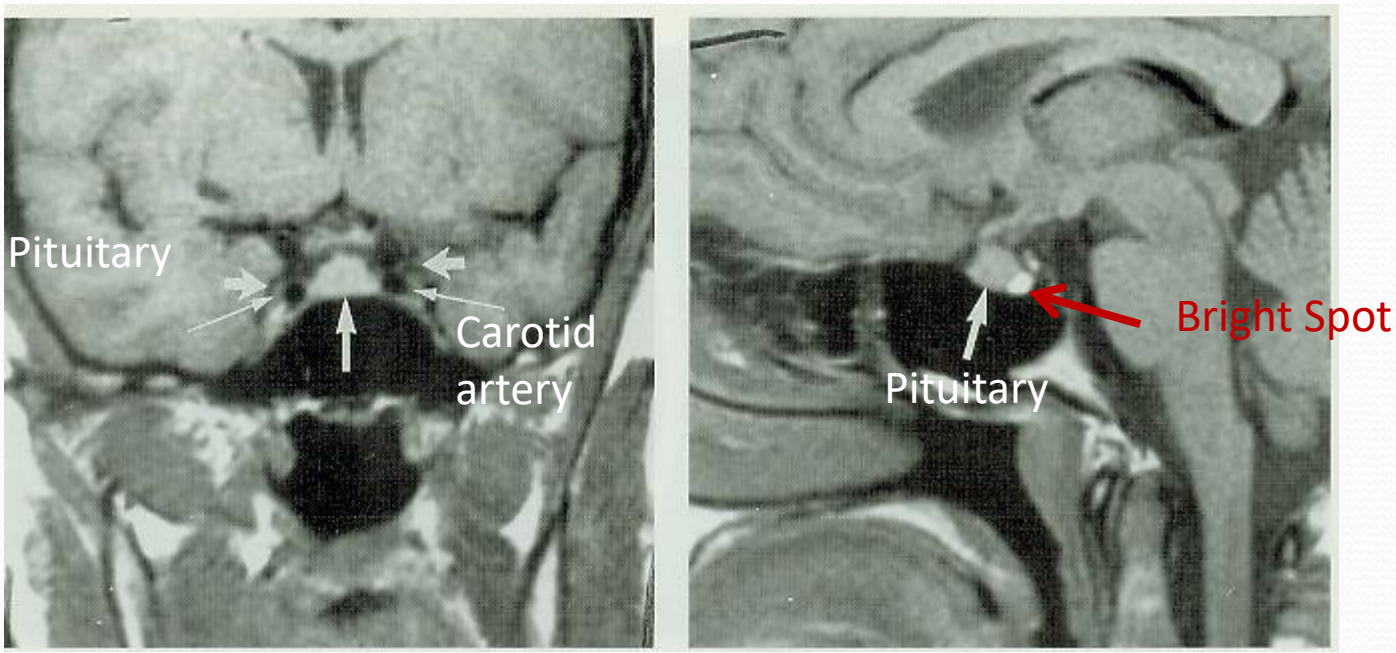
PITUITARY & FRIENDS
kidney
adrenal gland
muscle
ovary
ADH
ACTH
FSH LH
GH
testicle
MSH
FSH LH
skin
TSH
oxytocin
GH
oxytocin
prolactin
thyroid
uterus
liver
mammary gland

# Normal Hypothalamus-Pituitary

**A**denohypophysis

**N**eurohypophysis



# Testing

- Suppression tests

Used when HYPERfunction of the gland is suspected

  - Patient found to have excess cortisol
  - Dexamethasone suppression test
    - Administer dexamethasone (a synthetic glucocorticoid)

- Stimulation tests

Used when HYPOfunction of the gland is suspected

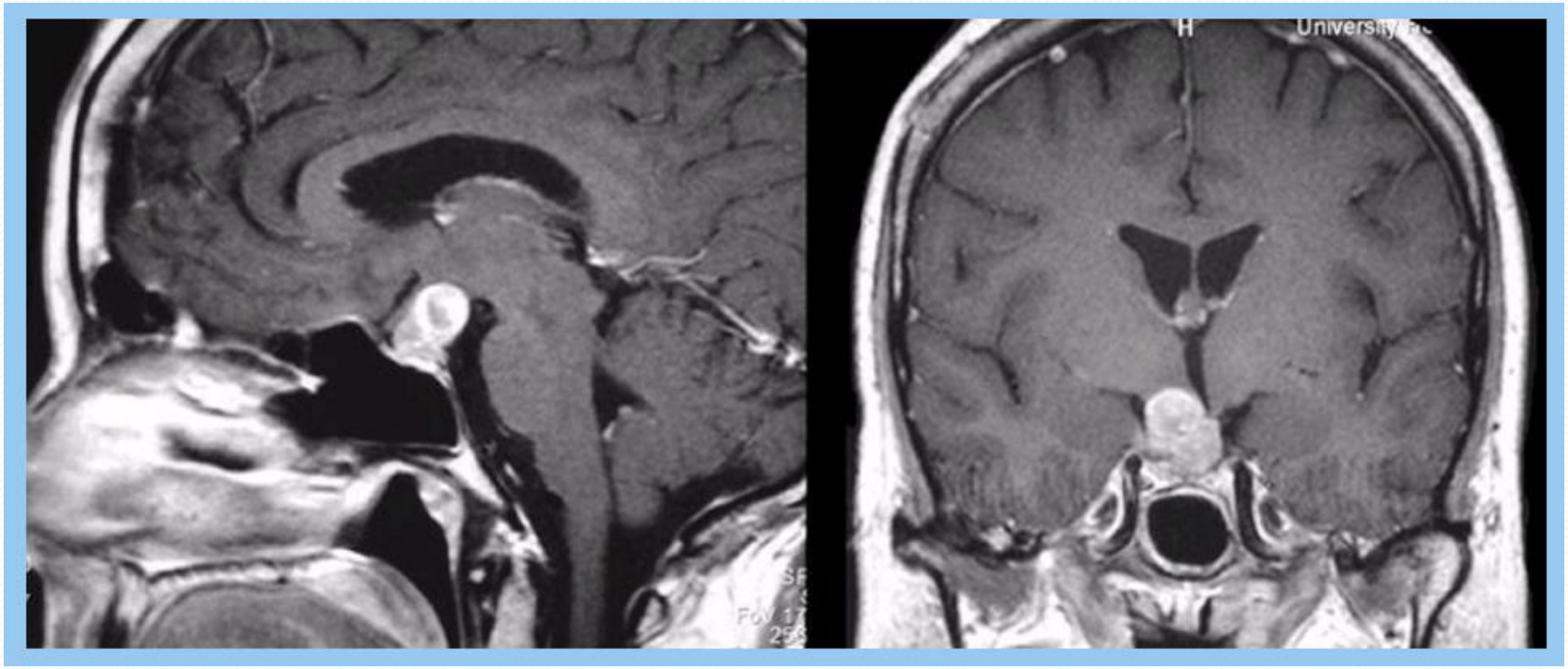
  - Patient found to have low cortisol
  - ACTH Stimulation test
    - Test adrenals response to synthetic ACTH

Pituitary macroadenomas: > 1 cm adenomas
Pituitary microadenomas: < 1 cm adenomas

# Case 1:

- A 50-year-old male with prior history of tension headache is evaluated for new onset headache that is different in character in comparison to tension headache. He stated that the headache is throbbing, and is now more frequent and respond poorly to any medication. His medical history is otherwise unremarkable.
- On physical examination, vital signs are normal. Physical examination including funduscopic examination is normal.

MRI reveals : 2 cm pituitary adenoma with suprasellar extension and displacing the optic chiasm and the hypothalamus.

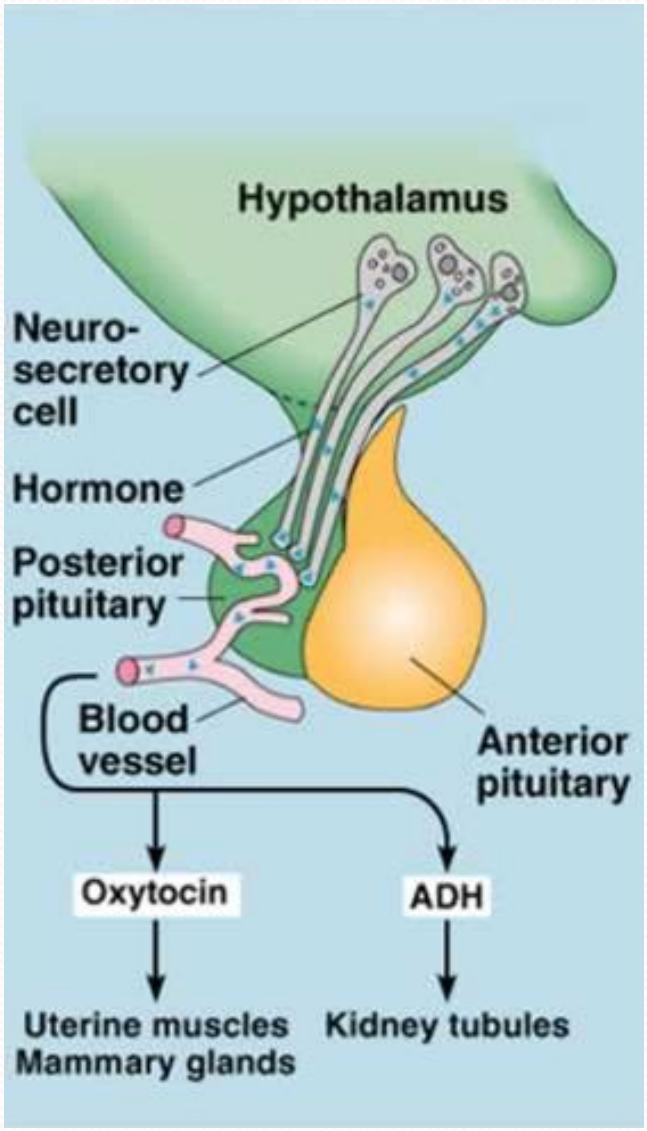


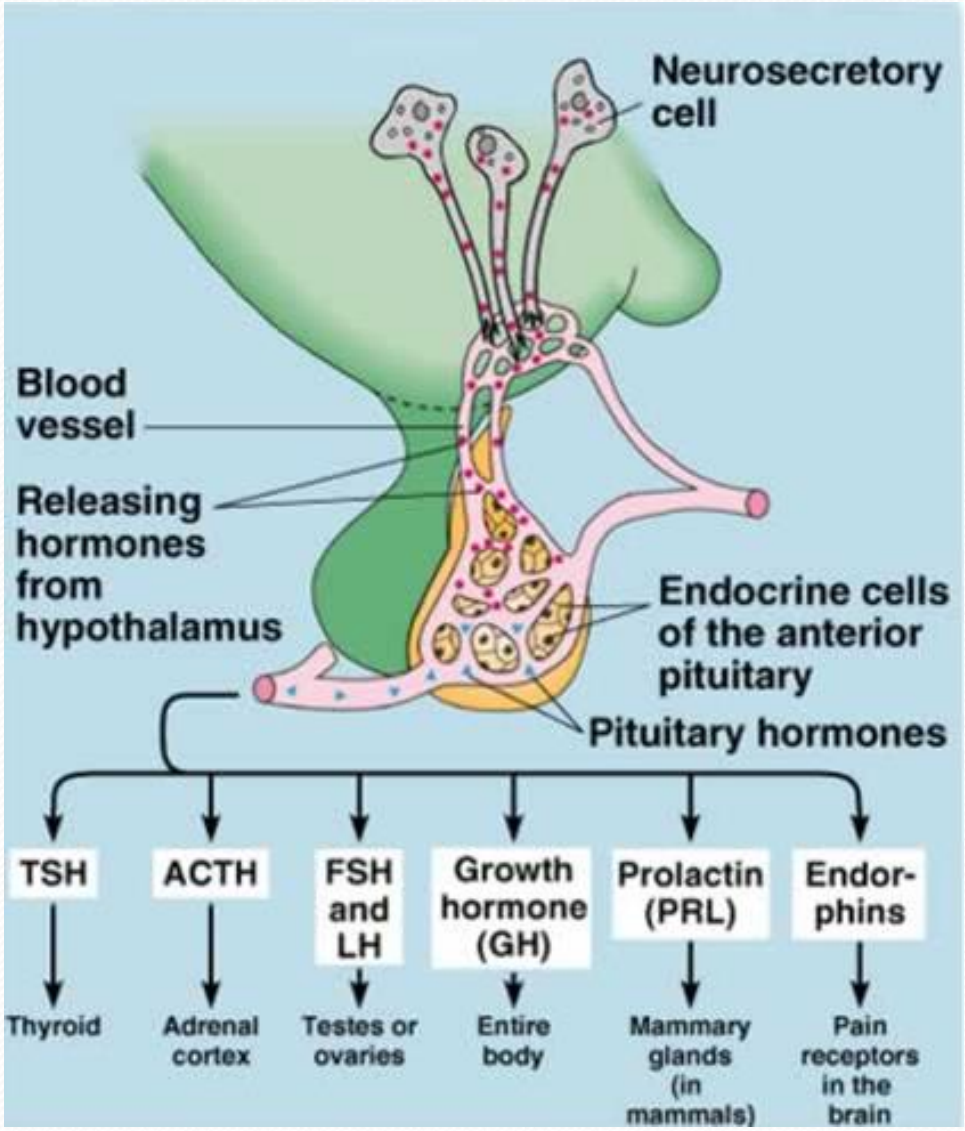
# A)What is the best next step in management?

A) Refer to neurology
B) Perform full pituitary hormonal panel
C) Refer for formal visual field testing
D) Start hydrocortisone
E) B+C
F) A+D

Answer: E Perform full pituitary hormonal panel and Refer for formal visual field testing

# Explanation:



# Disorders of pituitary

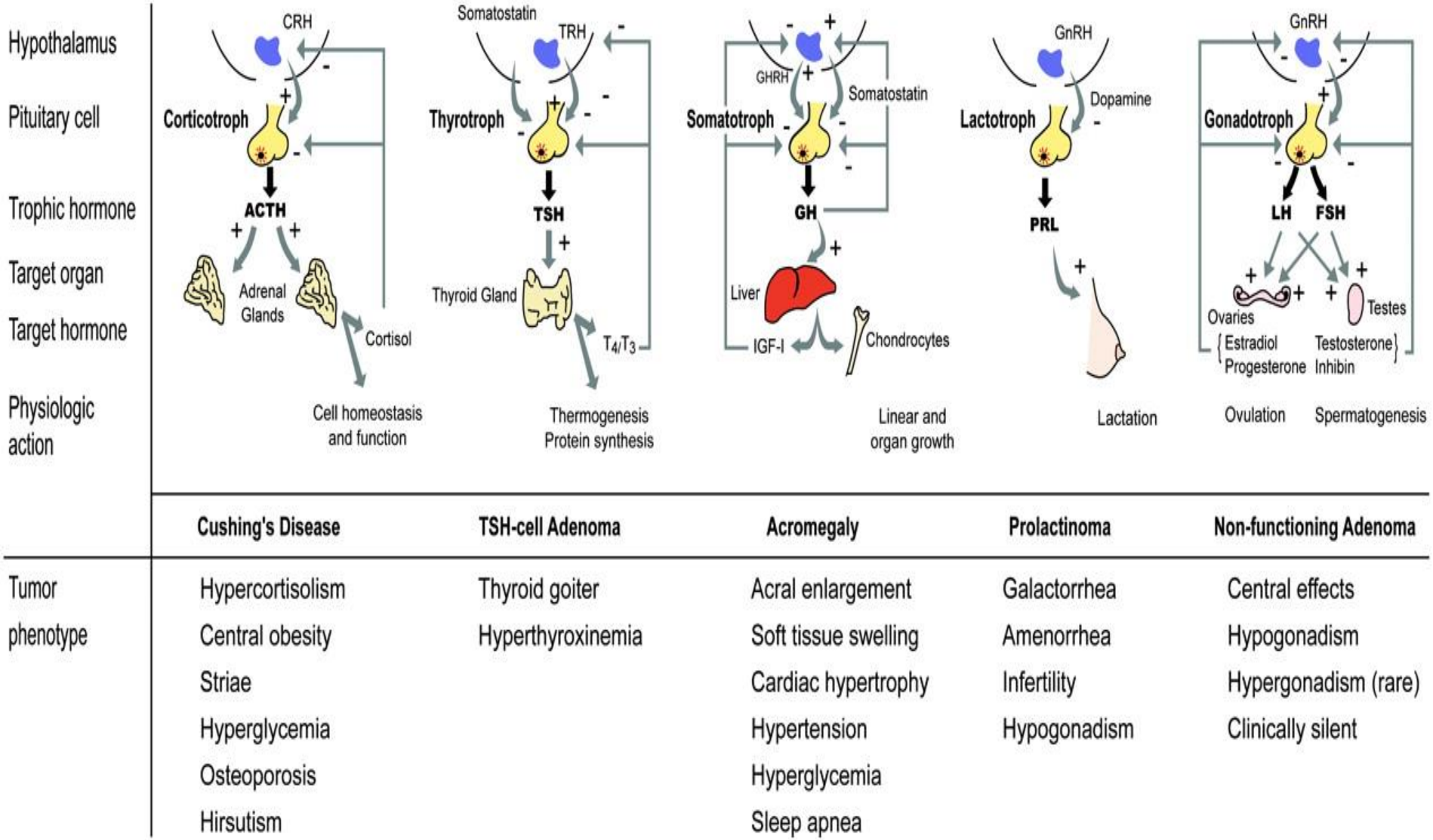
## Functional

- Excess growth hormone (Acromegaly)
- Pituitary dependant Cushing's Disease (ACTH)
- Prolactinomas with prolactin associated hypogonadism
- Central hyperthyroidism due to TSH secretion
- Rare increased LH or FSH with increase in T or $E_2$

## Anatomical

- Visual field loss, cranial nerve injury etc
- Hypopituitarism
- CSF leak etc
- Diabetes insipidus: uncommon

# Hypothalamic-pituitary regulation and pituitary tumor pathogenesis



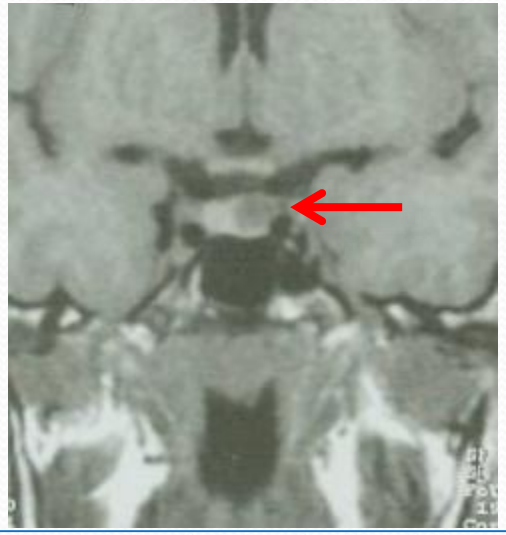

| | Cushing's Disease | TSH-cell Adenoma | Acromegaly | Prolactinoma | Non-functioning Adenoma |
|---|---|---|---|---|---|
| Tumor phenotype | Hypercortisolism | Thyroid goiter | Acral enlargement | Galactorrhea | Central effects |
| | Central obesity | Hyperthyroxinemia | Soft tissue swelling | Amenorrhea | Hypogonadism |
| | Striae | | Cardiac hypertrophy | Infertility | Hypergonadism (rare) |
| | Hyperglycemia | | Hypertension | Hypogonadism | Clinically silent |
| | Osteoporosis | | Hyperglycemia | | |
| | Hirsutism | | Sleep apnea | | |

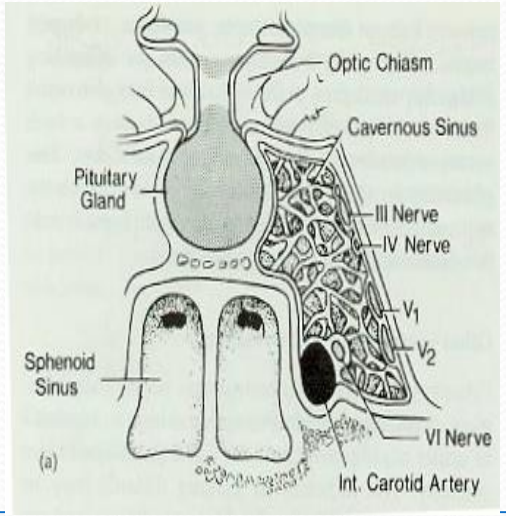
**Melmed, S. J. Clin. Invest. 2003;112:1603-1618**

| TYPE | Prevalence % | Hormone Staining | Clinical Manifestations |
|---|---|---|---|
| Prolactinoma | 40-45 | Prolactin | Signs of Increased Prolactin |
| Somatotroph Adenoma | 20 | GH +/- prolactin | Acromegaly |
| Corticotroph Adenoma | 10-12 | ACTH +/- others | Cushing's Disease |
| Gonadotroph Adenoma | 15 | FSH, LH αSU, βSU | Compression Sx Hypopituitarism |
| Null Cell | 5-10 | None | Compression Sx Hypopituitarism |
| Thyrotroph Adenoma | 1-2 | TSH,αSU, =/- GH | Hyperthyroidism Compression Sx |

# Non functioning Pituitary adenoma

*Not a bad idea to warn all patients before MRI of CNS*






Symptoms:

- Intrasellar: Headache, Pituitary hypofunction
- Tumor associated loss: GH>LH/FSH>TSH>ACTH
- Suprasellar: Impingement on Optic Chiasm
- Other Mass Effects: obstruction of 3rd ventricle, hydrocephalus, altered sensorium

➢ Lateral Extension: Impingement on Cr N iii, iv, vi

➢ Inferior Erosion: Spinal Fluid Leak, Meningitis

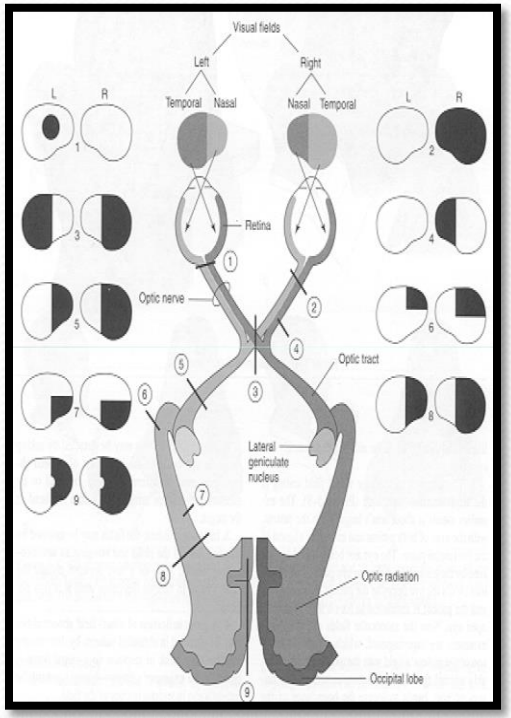
***Endo Society Recommendations for non functioning adenoma follow up :***

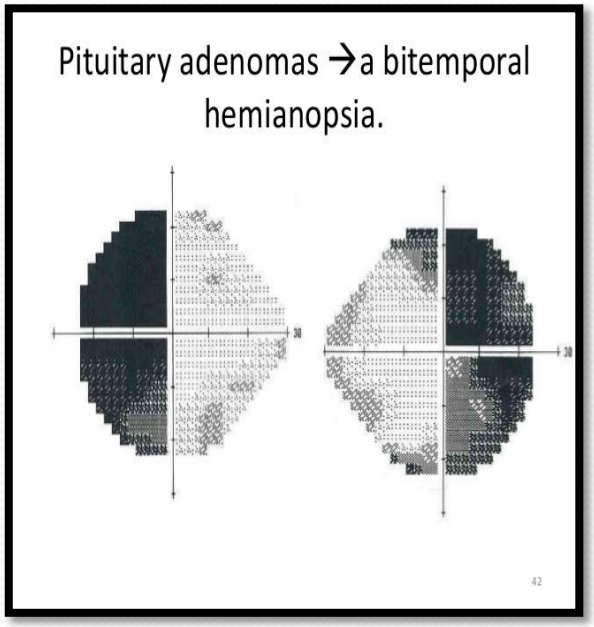
***<1cm - MRI in 1 year***

***> 1cm - 6 months then yearly x 3***

# Other tests for pituitary lesions

- All patients presenting with a pituitary incidentalomas compressing the optic nerves or chiasm on MRI should undergo formal ophthalmic examination *(Endo society strong recommendation, high-quality evidence)*
  - Visual field
  - Extraocular movements
  - Ophthalmoscopy – primary optic atrophy



# Case 2:

- A 35-year-old female with a past medical history with bipolar disorder,  had amenorrhea and galactorrhea for the past 2 months.  In addition, she complained of weight gain with worsening fatigue for the past 2 months. Her home medications including olanzapine. She also uses occasional opiates for chronic back pain.

# What is the best next step in management ?

A) Get serum estradiol with FSH and LH
B) Get serum prolactin level
C) Get serum TSH and free $T_4$ level
D) Stop the olanzapine
E) Advise her to stop the opiate
F) A+B
G) B+C

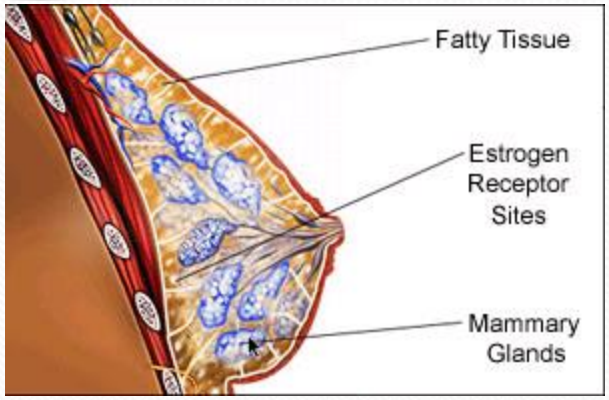
Answer is F: Get serum prolactin, TSH and free $T_4$ level.

If the prolactin level come back 80 ng/ml( reference range 2-20 ng/ml, what is the best next step in management?

A) Get serum pregnancy test
B) Get formal visual evaluation test
C) Get pituitary MRI
D) Get serum liver and kidney function tests

Answer: A) Get serum pregnancy test

# Prolactin




- Physiologic function of PRL includes:
  - Milk production
  - Metabolism of fats and carbohydrates
  - Vitamin D metabolism
  - Fetal development
- Main function of PRL is:
  - Mammary gland development (puberty)
  - Initiation of lactation postpartum (pregnancy)
- Secreted by lactotrophs of the anterior pituitary(in a pulsatile manner)

<u>Regulation:</u>

- ❑ *Inhibited by hypothalamic Prolactin Inhibitory Factor (dopamine)*
- ❑ *Stimulated by high Thyrotropin Releasing Hormone (TRH)*
- ❑ *Increased by chest wall motion and nipple stimulation*
  - *Smaller increases after sleep, exercise, intercourse, stress, pregnancy and lactation*
- ❑ *Suppresses GnRH → suppress LH and FSH*
- ❑ *Stimulates adrenal androgen production*

# Etiologies of Hyperprolactinemia

- Prolactinoma (autonomous production)
- Other pituitary tumors (GH, ACTH)
- Hypothalamic disease
- Chronic Kidney Failure (decreased clearance by kidneys) or Liver Disease
- Spinal cord
- Chest wall
- Severe Prin
- Medication
  - Anti-p
    Reglan
  - Dopamine-"depleting" agents (methyldopa, reserpine)
  - Others (INH, danazol, tricyclic antidepressants, verapamil, estrogens, antiandrogens, cyproheptadine, opiates, H2-blockers)
- Radiation, Surgery
- Idiopathic , Pregnancy

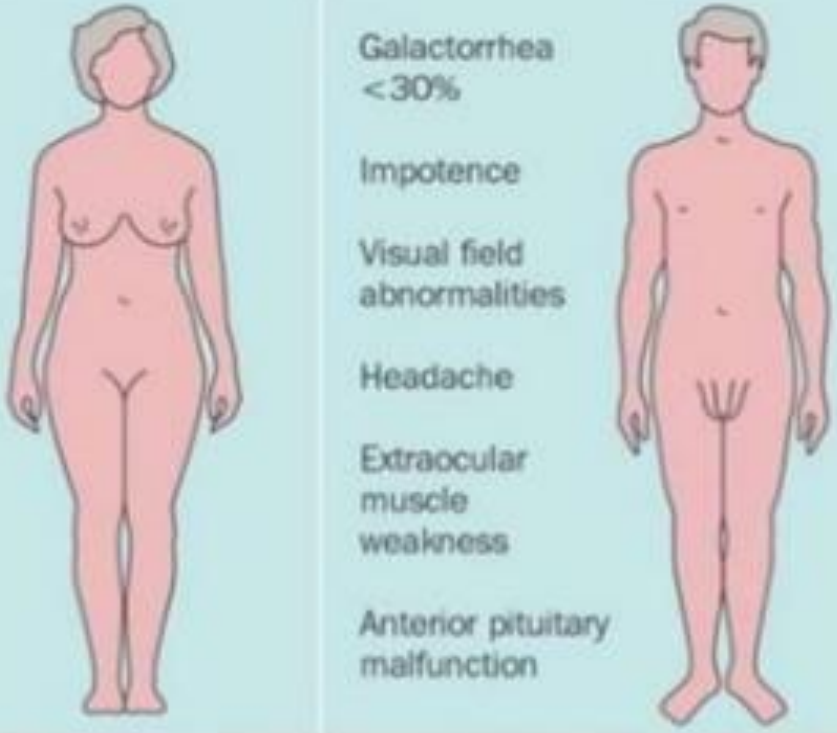
Testing:

- Serum assays: Fasting PRL, FSH, LH, estradiol, testosterone, TSH, renal/hepatic panels, and ß-hCG in females
- MRI of pituitary and brain
- Visual field examination/Neurological testing-if mass effect suspected

and

# Clinical manifestations of hyperprolactinemia

| Women | Men |
| --- | --- |
| Galactorrhea 30–80% | Galactorrhea <30% |
| Menstrual irregularity | Impotence |
| Infertility | Visual field abnormalities |
| | Headache |
| | Extraocular muscle weakness |
| | Anterior pituitary malfunction |



Microadenoma seen more in women

Macroadenomas seen more in men

- Hypogonadism in both women and men by supressing GnRH secretion and pulsutility, resulting in low levels of LH and FSH

# NEUROENDOCRINE PHARMACOLOGY

Prolactin Inhibitory Factor – Dopamine

- Prolactin is under tonic *inhibitory* control and predominant inhibitor is dopamine
- D2 receptors are coupled to G-proteins and increase intracellular C-AMP
- Growth hormone secreting tumors may also express D2 receptors

**Treatment:**

- First line of treatment is Dopamine agonists (may have dramatic effects on prolactin secreting tumors)
- Cabergoline (weekly) or bromocriptine (twice daily)
- Microadenomas respond dramatically; often with resumption of menses and restoration of fertility
- +/- surgical resection

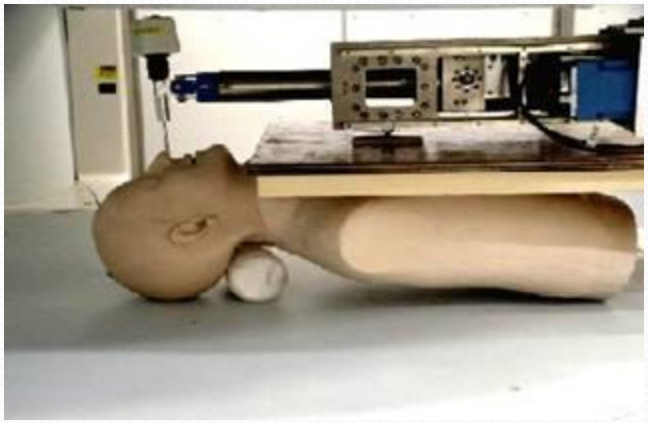
## Dopamine Agonists

- *Bromocriptine:* excellent drug with strong record of clinical success; drug of choice in infertility; troublesome side effects can occur.(Daily medication)
- *Cabergoline*: most tolerable preparation with less side effects biweekly dosing;

*NB: High doses of cabergoline and pergolide( in Parkinsonism) are associated with valvular heart disease due to activation of valvular serotonin receptors → so echocardiography is required for follow up*

# Treatment of Prolactinemia and Prolactinoma

- Transsphenoidal resection
- Surgical resection
- Radiation therapy



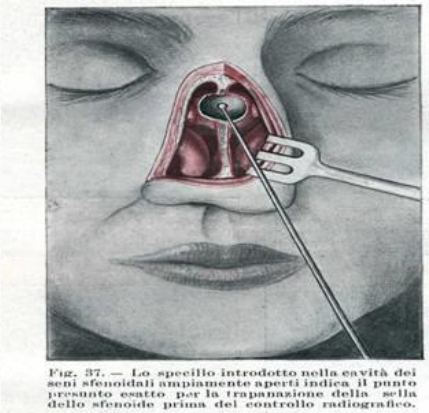


Fig. 37. — Lo specillo introdotto nella cavità dei seni sfenoidali ampiamente aperti indica il punto presunto esatto per la trapanazione della sella dello sfenoide prima del controllo radiografico.

# Pregnancy and prolactinoma

1) What medication can be used in pregnancy?
2) Do we stop the bromocriptine/Cabergoline if the patient become pregnant
3) How to follow up patients off medication during pregnancy

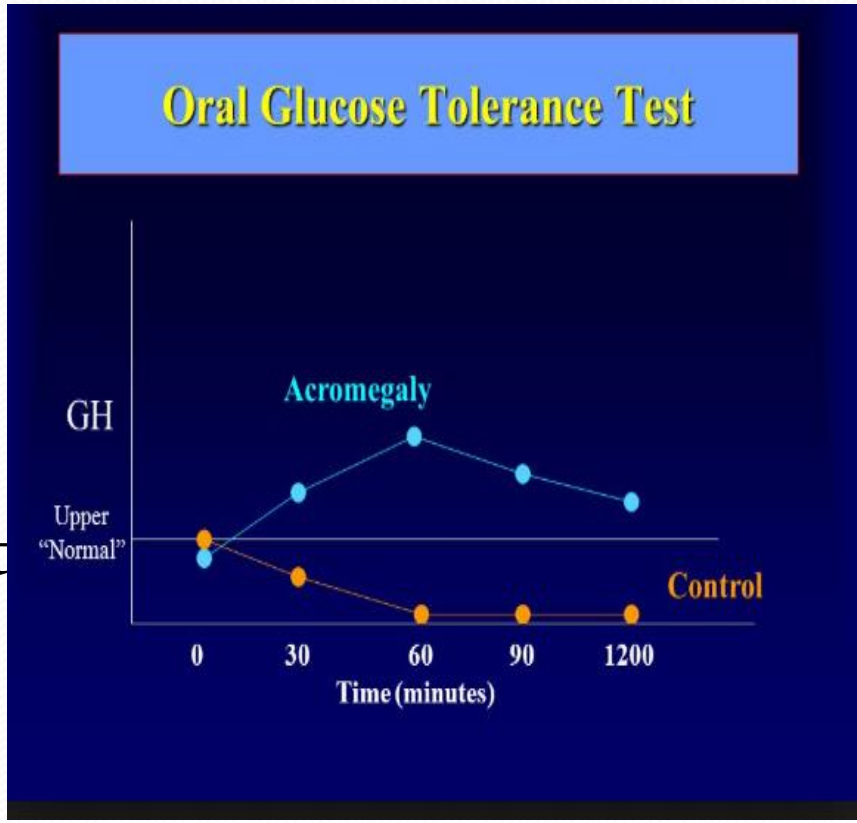
Extra question: What is the treatment of asymptomatic prolactinoma in a patient who doesn't wish to become pregnant?

# Case 3

- A 55 years old with a past medical history of obstructive sleep apnea, hypertension , carpal tunnel syndrome and type 2 diabetes complained of chronic headache and fatigue. Physical examination revealed coarse facial features with frontal bossing and macroglossia.
- Laboratory testing showed
- IGF1 1500 ng/ml( references 72-207 ng/ml) with hemoglobin A1C 10% and prolactin 50 ng.ml
- Normal am cortisol, FSH, LH, testosterone, TSH, free T4 , ACTH level.

# What is the best next step in management ?

- A) Insulin tolerance test
- B) Glucagon stimulation test
- C) Oral glucose tolerance test
- D) Get serum Growth hormone
- E) Arginine GnRH stimulation t




Answer:C) Oral glucose tolerance test

# Physiology of GH

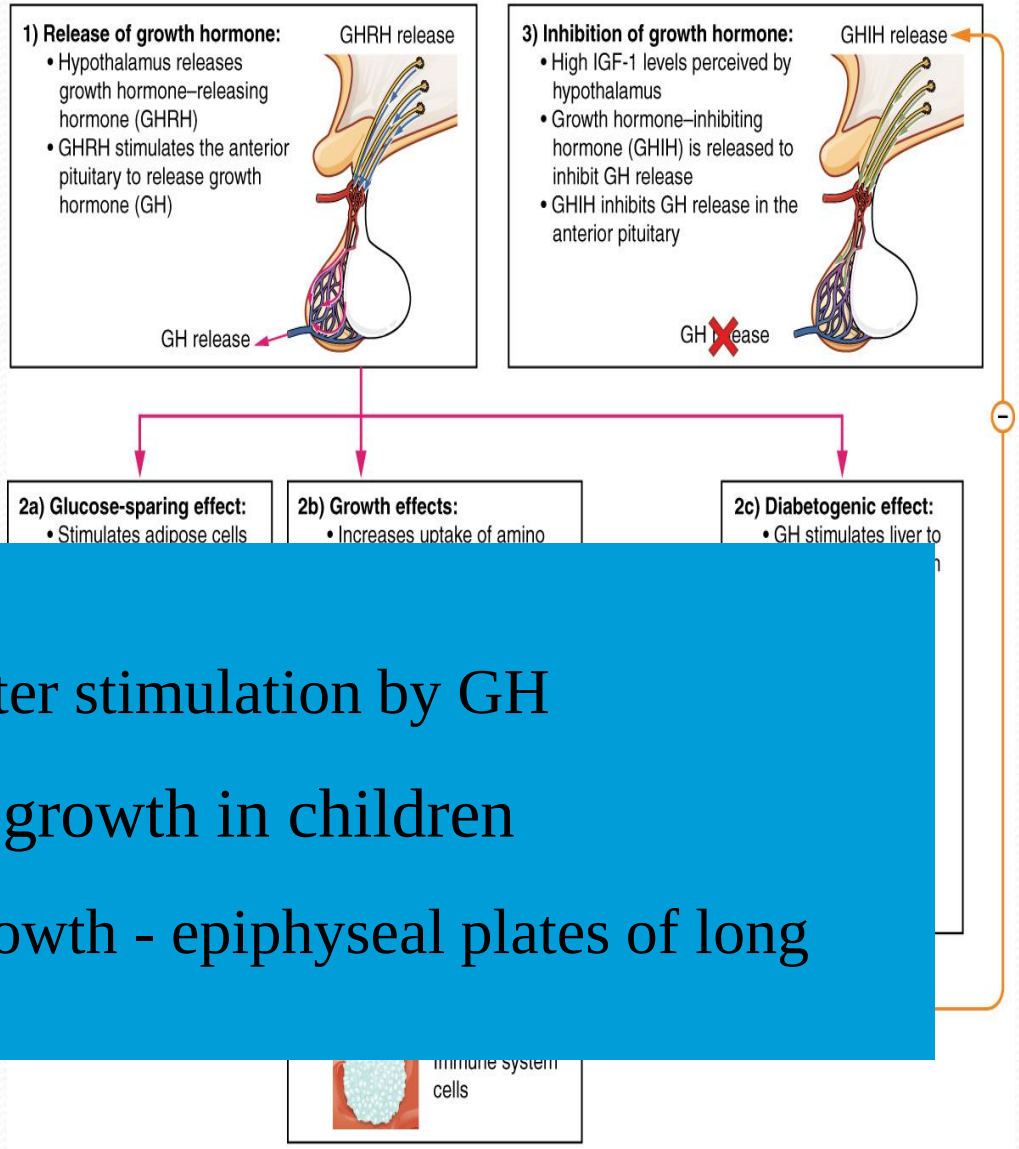
Growth hormone (GH) - most abundant pituitary hormone - somatotrope cells

GH secretion - controlled by hypothalamic and peripheral factors

- GHRH – stimulates GH
-

GH se
undete

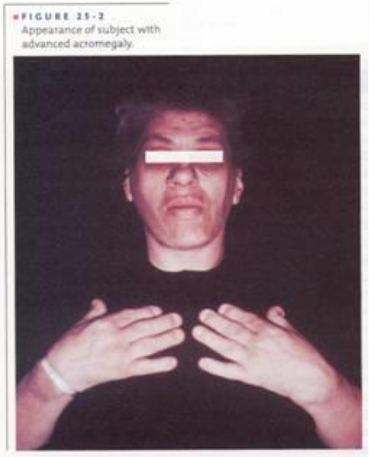
Peak G
the on




- IGF-1
  - produced in liver after stimulation by GH
- GH stimulates linear growth in children
  - IGF-1 stimulates growth - epiphyseal plates of long bones

# Acromegaly

- Clinical syndrome of hypertrophic and degenerative injury to soft tissues, joints, the heart and cardiovascular system accompanied by disturbances in respiration and intermediary metabolism.
- Macroadenoma in > 70 %
- Onset of Sx 10 – 12 years before diagnosis
- Excessive growth hormone (GH) after puberty




- Incidence – 3-4 per million/yr and Mean age - 40-45 years
  - *Diagnosis delayed due to slow progression of signs and symptoms*
- Most common cause - GH secreting adenoma of the pituitary

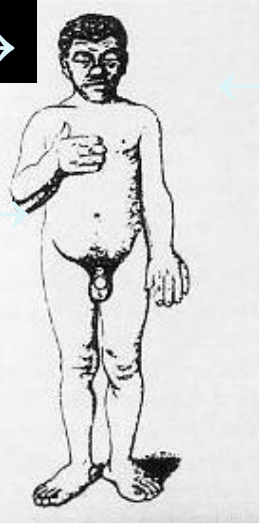
# Acromegaly – Systemic Abnormalities

- Visceromegaly
- PulmonaryAbnormalities: OSA and Narcolepsy
- Mineral and Electrolyte Abnormalities
  - Low Renin and Increased Aldosterone
  - Hypercalciuria (Kidney stones common)
  - Herpervitaminosis 25 D
- Skin and Gastrointestinal Systems: Skin Tags and Colonic Polyps
- Cardiovascular: CHF , HTN and Cardiomyopathy
- Reproductive Abnormalities
- Carbohydrate and Lipid Abnormalities: DM and Hypertriglyceridemia

*Hyperprolactinemia (30% may be over 200 ng/L)*

# ACROMEGALY

Frontal Bossing →

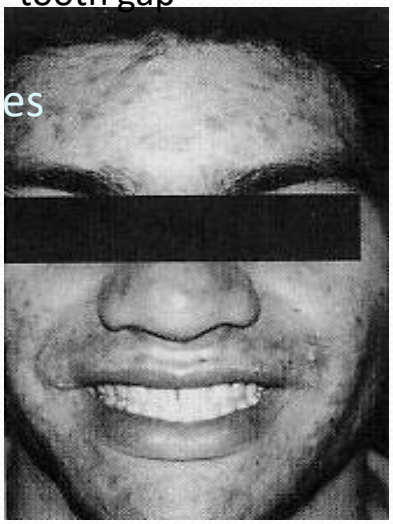


←Facies

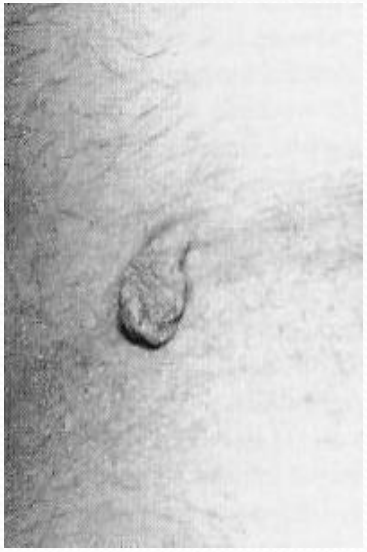
Fleshy → fingers

Fleshy toes→

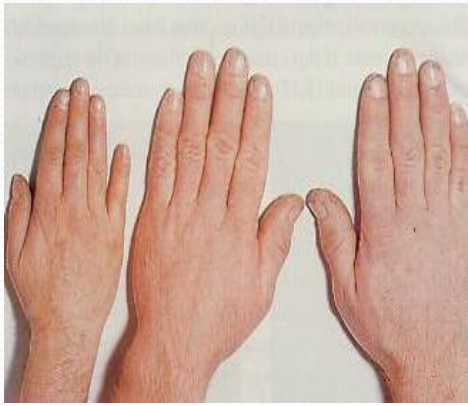
Active perspiration, oily skin, acne, wide tooth gap



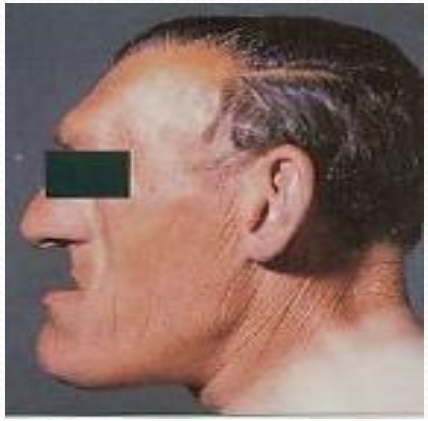
Prominent skin tags may be associated with colonic polyps



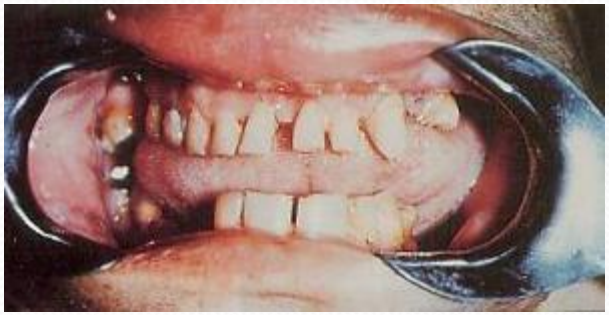
Acromegalic hands



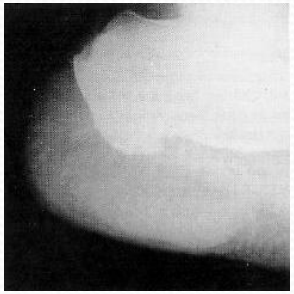
Prognathism, Frontal bossing



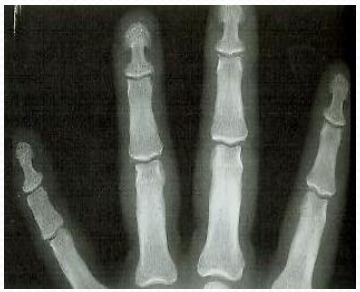
Mandibular growth results in increased tooth separation



Increased heal pad thickness (> 22mm)



Distal tufting of the terminal phalanges



# Summary of Clinical Manifestations of Acromegaly

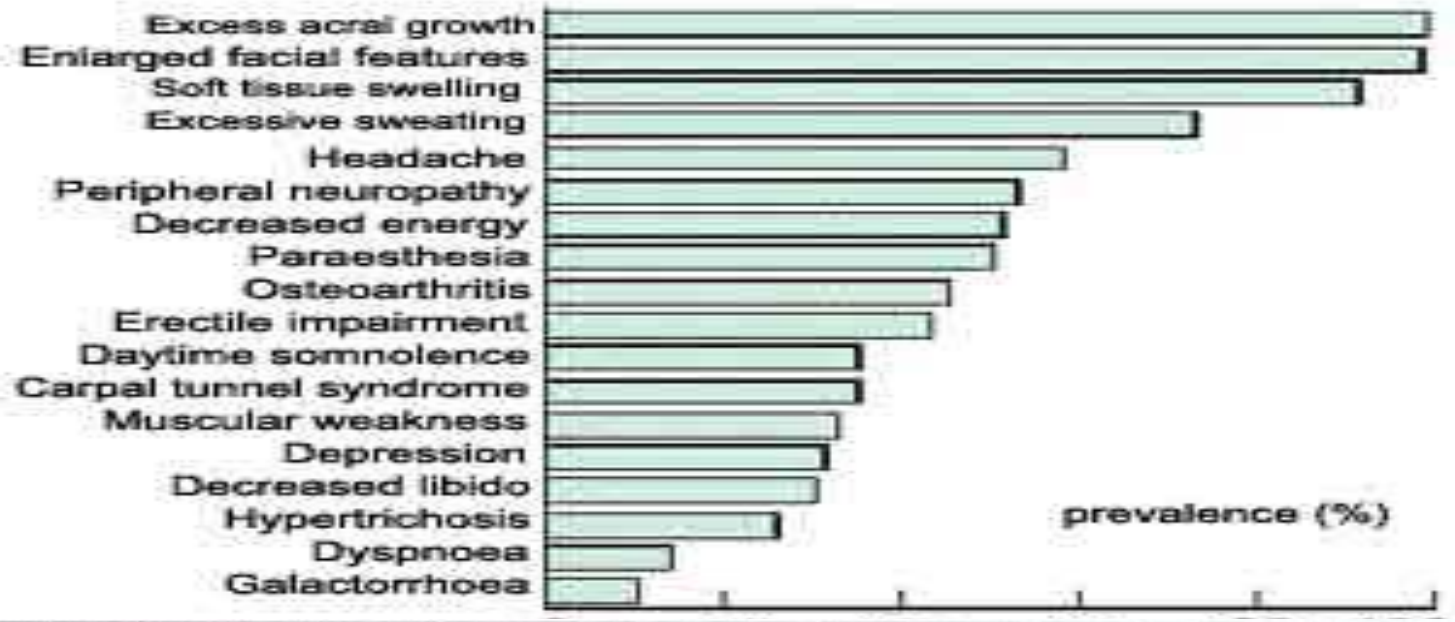
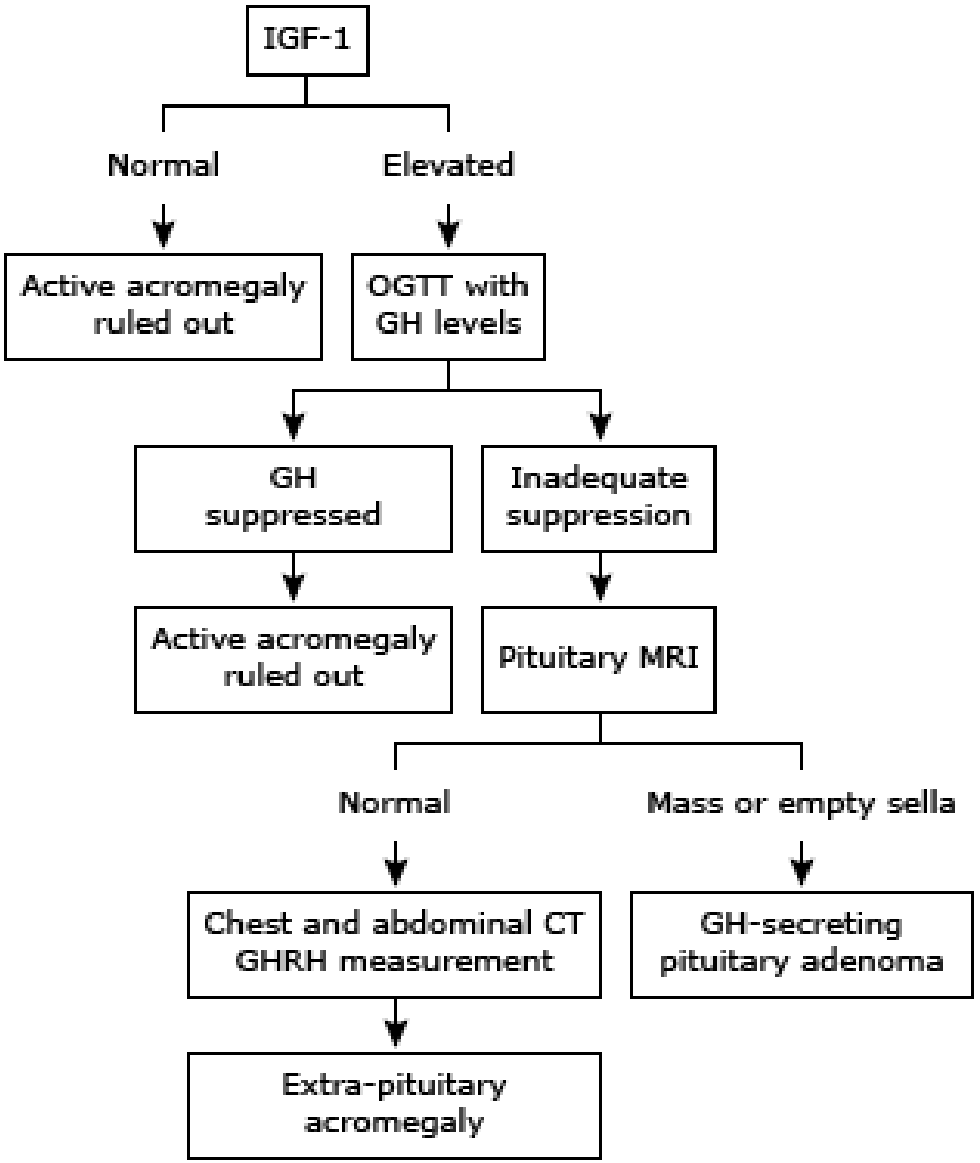



**Table 3-1. Manifestations of Acromegaly**

| |
|---|
| **Skeletal and soft tissue changes** |
| Enlargement of hands (especially fingertips) and feet |
| Increased ring, glove, shoe size |
| Coarsening of facial features |
| Thick skinfolds: brow, nasolabial creases |
| Enlargement of nose and mandible, with prognathism, spreading of teeth |
| Enlargement of internal organs: heart, lungs, liver, spleen, kidneys |
| Skin thickening and interstitial edema, with swelling and firmness of soft tissue |
| Osteoarthritis |
| Entrapment neuropathies, especially carpal tunnel syndrome |
| X-ray changes: enlargement of sinuses, tufting of distal phalanges, cortical thickening |
| **Metabolic changes** |
| Decreased glucose tolerance (anti-insulin actions of growth hormone) |
| Hyperphosphatemia (increased tubular reabsorption of phosphate caused by growth hormone) |

# Algorithm for the diagnosis of acromegaly

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# Acromegaly treatment

1)Surgical treatment :Trans-sphenoidal surgery is the treatment of choice

2) Adjuvant Radiation therapy→ can lead to panhypopituitarism

3) Medical:

- Somatostatin and Somatostatin Analogues
  - **octreotide**: short acting somatostatin analogue interacts with SSTR2 and SSTR5 which are expressed in 90% of growth hormone secreting tumors
  - **octreotide LAR**: long acting release preparation given monthly
  - **lanreotide gel**: now available in US similar activity to octreotide
  - **pasireotide:** potent analog, especially useful in Cushing's Disease; effective against wider range of SST's and associated with hyperglycemia
- Bromocriptine, a dopamine analog, was the agent used most commonly until recently
- Growth Hormone receptor antagoniosts
- Combination therapy - bromocriptine and octreotide

# Long Term Management

- Clinical evaluation and assessment of GH secretion : Evaluate every 3-4 months
  - Clinical exams
  - Serum IGF-1
  - OGTT
- Adenoma size
  - MRI - repeat yearly for the first several years after surgery
  - Semiannual visual field assessment
    - Visual problems before surgery, Macroadenomas and Residual extra-sellar adenoma after surgery
- Systemic evaluation
  - Colonoscopy at 3 to 4 year intervals in patients over 50 years
  - Annual cardiovascular evaluation ( echocardiography)
  - Thyroid Ultrasound to rule out nodules and cancer
  - Sleep studies to rule out OSA
  - Other systemic manifestation as Fasting blood glucose, A1C , lipid profile, assessment of anterior pituitary hormones panel (TSH , am cortisol)

# Summary of Treatment of Pituitary and Hypothalamic Tumors

- SURGERY:
  - **Microadenomas** (<10 mm):Transphenoidal Surgery
  - **Macroadenomas** (>10 mm): surgical cure less likely
  - **Giant Pituitary Tumor** (30-40mm): extremely difficult
  - **Hypothalamic Tumors** (Craniopharyngioma) TSS or Transfrontal approach
- RADIATION THERAPY
  - Conventional Radiation
  - Stereotactic Radiosurgery (Gamma Knife)
    Highly focused single dose radiation
- PHARMACOLOGIC THERAPY
  - Somatostatin Analogues
    - Acromegaly, TSH Secreting tumors
  - Growth Hormone Receptor Antagonists
    - Acromegaly (Pegvisomant)
  - Dopaminergic Agonists
    - Prolactinoma, Acromegaly

# Case 4:

- A 42 years old man reports fatigue, weight gain ,decrease libido and erectile dysfunction associated with mild headache for the past year. He has been well until these symptoms started. On physical examination, he had no significant abnormalities aside from being overweight with delayed deep tendon reflex.
- Laboratory test results:
  - Normal CBC, BMP, prolactin
  - TSH 0.3 mIU/L( reference 0.5-5 mIU/l) , free T4= 0.5 ng/dl(0.8-1.8 ng/dl), Total testosterone 121 ng/dl( reference 300-700 ng/dl) with suppressed FSH and LH
- MRI showed partial empty sella

# What is the best next step in management ?

A) Start levothyroxine replacement therapy
B) Get repeat am testosterone level
C) Get am cortisol level with ACTH level
D) Get IGF 1 level
E) Get GH level
F) A+C+E
G) B+C+D

Answer: G: Get am cortisol level with ACTH level, IGF1 and repeat and testosterone level.

Don't start levothyroxine unless Adrenal insufficiency is excluded

# Causes of hypopituitarism

| **Hypothalamic diseases** |
| --- |
| Mass lesions – Benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc) |
| Radiation – For CNS and nasopharyngeal malignancies |
| Infiltrative lesions – Sarcoidosis, Langerhans cell histiocytosis |
| Infections – Tuberculous meningitis |
| Other – Traumatic brain injury, stroke |
| **Pituitary diseases** |
| Mass lesions – Pituitary adenomas, other benign tumors, cysts |
| Pituitary surgery |
| Pituit |
| Infiltr |
| Infec |
| Infar |
| Apoplexy |
| Genetic mutations |
| Empty sella |

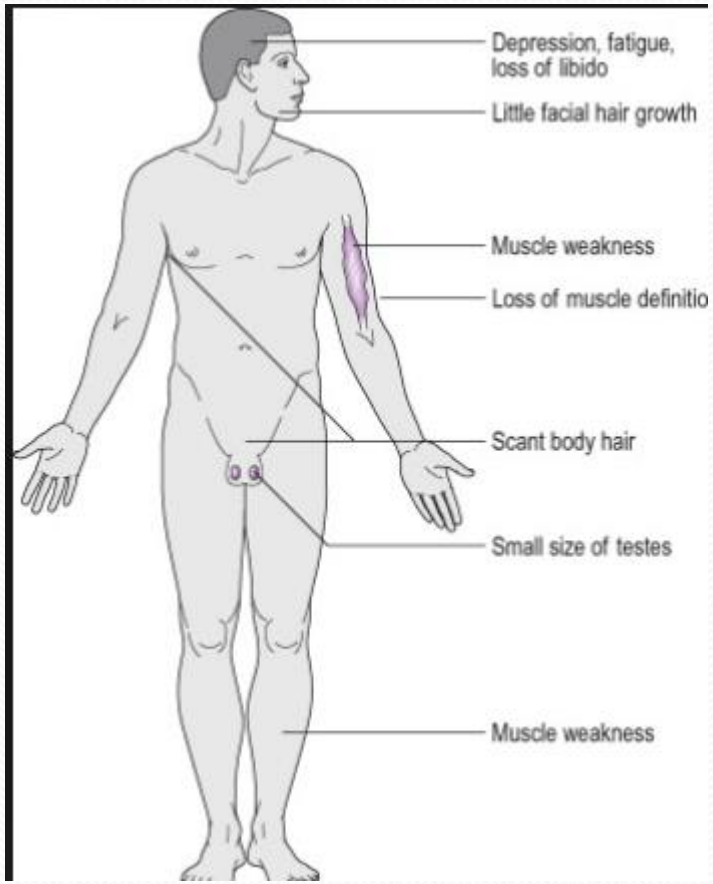
Ipilimumab is a check point inhibitor that has been associated with hypophysitis in 17% of the patients.

It can also induce autoimmune adrenalitis and hypothyroidism.

# Evaluation of Hypopituitarism

## A)Hypogonadism

- Men: low libido, impaired fertility, decreased muscle mass and strength
- Women: **abnormal menstrual history**, infertility, low libido, further loss of body hair if in conjunction with adrenal insufficiency
- Labs: decreased LH & FSH, low testosterone( in males), low Estrogen ( in Females)

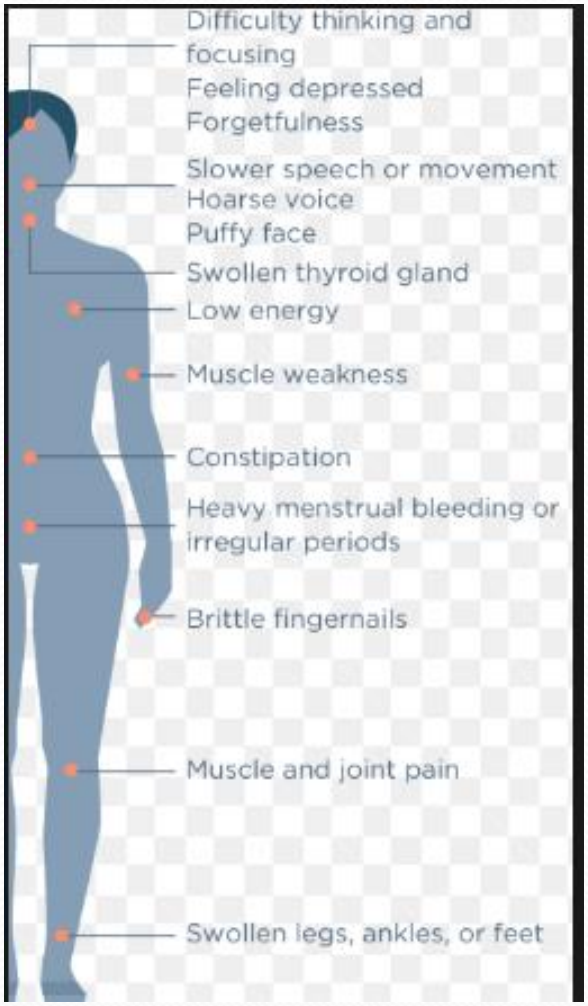


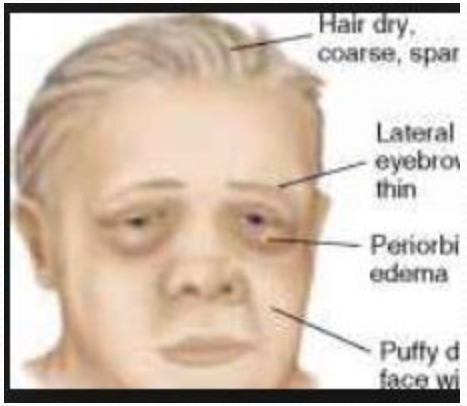
# Evaluation of Hypopituitarism

## B)Hypothyroidism

- Signs & symptoms: fatigue, cold intolerance, constipation, slow relaxing reflexes
- Hyponatremia (exacerbated by cortisol deficiency), normocytic anemia (exacerbated by secondary hypogonadism and GH deficiency)
- Low FT4, low or inappropriately normal TSH

Remember that we follow up Free T4 when we gave thyroid replacement therapy ( unlike primary hypothyroidism when you follow up by normalization of TSH level )



# Evaluation of Hypopituitarism

# C)Adrenal insuffiency

- Symptoms: fatigue, weakness, dizziness, nausea, vomiting, hypotension, hypoglycemia
- Hyponatremia (particularly if also TSH deficiency)
- Treatment by replacement with prednisone ( no need of fludrocortisone)


- Remember that central adrenal insufficiency has normal aldosterone production so no hyperkalemia and since ACTH level is suppressed , no hyperpigmentation in contrary to primary adrenal insufficiency/Addison disease)
- Educate your patient about sick days rule (double or triple the dose for 3 days)
- Remember to prescribe emergency kit/Dexamethazone injection

# Evaluation of Hypopituitarism

## C)Adrenal insufficiency

- Laboratory testing
  - Screen AM cortisol
    - Cortisol < 5 mcg/dL: highly suggestive of adrenal insufficiency
    - Cortisol > 15: unlikely adrenal insufficient
    - Cortisol 5-15: equivocal → ACTH stimulation test
  - ACTH stimulation test (alternative - insulin tolerance test)
    - Baseline, 30 minutes, 60 minutes
    - Test is abnormal if stimulated cortisol < 18
  - Baseline ACTH low or inappropriately normal in setting of low cortisol

# Evaluation of Hypopituitarism D)Growth Hormone deficiency

- Reduced exercise capacity, central adiposity, hyperlipidemia, reduced bone remodeling activity
- Screening: IGF-1 < 2 standard deviations is suggestive
- Insulin tolerance test (alternatives – GHRH + arginine, glucagon)
  - Not needed if demonstrate 3 other pituitary hormone deficiencies (AACE 2016, ENDO 2011, GRS 2007)

<u>Treatment :</u>

Most common preparations subcutaneous administration Somatropin

Most available in multiple-dose pen devices

Daily therapy or three times a week( Depot is also available)


Humatrope Pen

# Case 5:

- A 67-year-old man is evaluated for headache, fatigue, and weakness for the past several weeks. Medical history is significant for metastatic melanoma that is being treated with ipilimumab, which is his only medication. On physical examination, vital signs are normal with normal exam except for a well-healed excisional scar on his posterior right shoulder. MRI shows enlarged pituitary with homogeneous enhancement. There is no compression of the optic chiasm.
- Laboratory studies:
  - Cortisol (8 AM) 3 µg/dL (82.8 nmol/L)
  - Prolactin 12 ng/mL (12 µg/L)
  - Thyroid-stimulating hormone 0.2 µU/mL (0.2 mU/L)
  - Thyroxine ($T_4$), free 0.6 ng/dL

# Which of the following is the most likely cause of this patient's findings?

- A) Ipilimumab-induced hypophysitis
- B) Lymphocytic hypophysitis
- C) Pituitary adenoma
- D) Primary hypothyroidism

Answer: A) Ipilimumab-induced hypophysitis


# Thanks for your attention

# Thank You!

CME SEMINARS