MEDICINE

432 Team

41 Pituitary Insufficiency

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

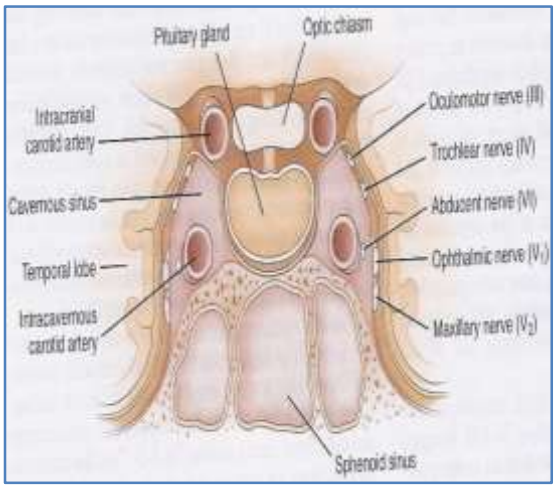
Objectives

Not Given :(

Pituitary gland

Development

- Anterior pituitary is recognizable by 4-5 weeks of gestation
- Full maturation by 20 week
- From Rathke's pouch, Ectodermal evagination of oropharynx
- Migrate to join neurohypophysis
- Portion of Rathke's pouch →→ Intermediate lobe
- Remnant of Rathke's pouch cell in oral cavity →→ pharyngeal pituitary
- Lies at the base of the skull as sella turcica
- Roof is formed by diaphragma sellae (Diaphragma sella is formed by a reflection of dura matter preventing CSF from entering the sella turcica by this diaphragm)
- Floor by the roof of sphenoid sinus
- Posterior pituitary from neural cells as an outpouching from the floor of 3rd ventricle
- Pituitary stalk in midline joins the pituitary gland with hypothalamus that is below 3rd ventricle
- Development of pituitary cells is controlled by a set of transcription growth factors like pit-1, Prop-1, Pitx2 (Normal pituitary stalk length 5- 7 mm, 2-3 mm in diameter)
- Pituitary stalk and its blood vessels pass through the diaphragm
- Lateral wall by cavernous sinus containing III, IV, VI, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers. Both adjacent to temporal lobes
- Pituitary gland measures 15 X 10 X 6 mm, weighs 500 mg but about 1 g in women (Height is 5-7 mm and 10 mm lateral dimension, height is 10. superior, middle supply ant. Pituitary. Inferior supply stalk and post pituitary artery)
- Optic chiasm lies 10 mm above the gland and anterior to the stalk
- Blood supply: superior, middle, inferior hypophysial arteries (internal carotid artery) running in median eminence from hypothalamus
- Venous drainage: to superior and inferior petrosal sinsuses to jugular vein



	Corticotroph	Gonadotroph	Thyrotroph	Lactotroph	Somatotroph
Hormone	POMC, ACTH	FSH, LH	TSH	Prolactin	GH
Stimulator	CRH, AVPm gp-130 cytokines	GnRH, Estrogen	TRH	TRH, Estrogen	GnRH, GHS
Inhibitor	Glucocorticoides	Sex steroids, inhibin	T3, T4, dapamin, somatostatin, GH	Dopamine	Somatostatin, IGF1, activins
Target gland	Adrenalin	Ovary and testes	Thyroid	Breast and other tissues	Liver, bone and other tissues
Trophic effect	Steroid production	Sex steroids, follicular growth and germ cells maturation	T4 synthesis and secretion	Milk production	IGF1 production, Growth induction and Insulin antagonist

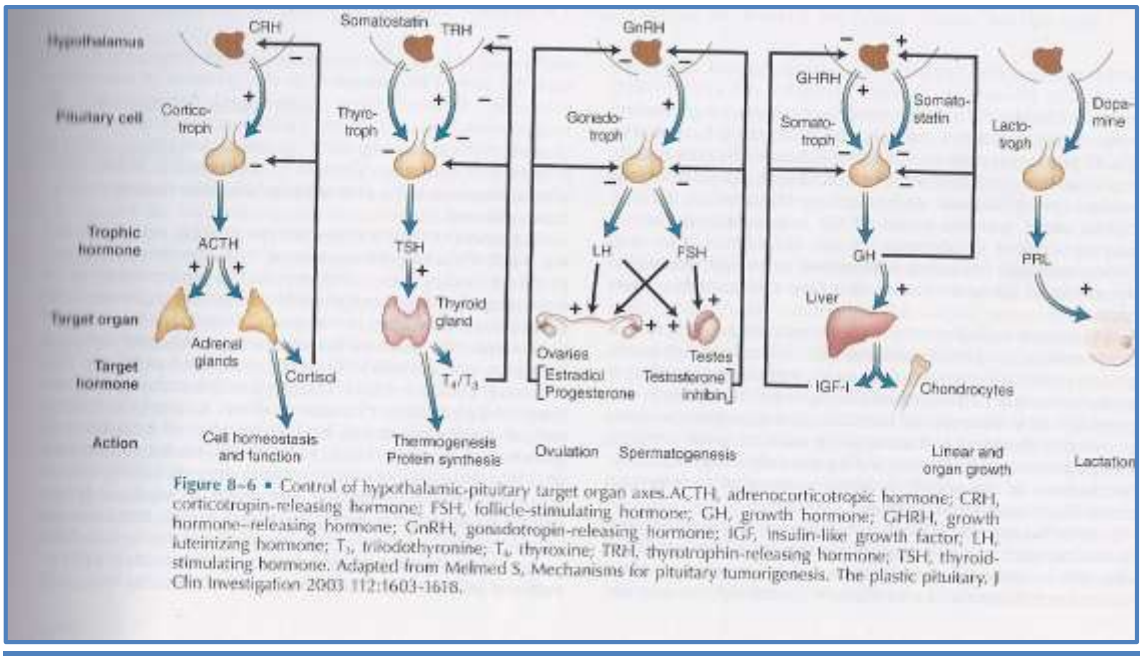


Figure 8–6 • Control of hypothalamic-pituitary target organ axes.ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone. Adapted from Melmed S, Mechanisms for pituitary tumorigenesis. The plastic pituitary. J Clin Investigation 2003 112:1603-1618.

Anterior Pituitary:

Growth Hormone, Gonadotrophs (FSH, LH), TSH, Prolactin and Corticotropin ACTH

Posterior Pituitary:

Oxytocin

Vasopressin

Disorders

- Non-functional pituitary tumor mass-effect
- Prolactin secreting cell disorder: prolactinoma
- Growth hormone secreting cell disorder: acromegaly
- ACTH secreting cell disorders: cushing's
- TSH secreting cell tumor: TSHoma
- Gonadotropin secreting cell disorder
- Diabetes Insipidus

Etiology of Pituitary masses:

- **Non-Functioning Pituitary Adenomas**
- **Endocrine active pituitary adenomas**
  - Prolactinoma
  - Somatotropinoma
  - Corticotropinoma
  - Thyrotropinoma
  - Other mixed endocrine active adenomas
- **Malignant pituitary tumors:** Functional and non-functional pituitary carcinoma
- **Metastases in the pituitary (breast, lung, stomach, kidney)**
- **Pituitary cysts:** Rathke's cleft cyst, Mucocoeles, Others
- **Empty sella syndrome**
- **Pituitary abscess**
- **Lymphocytic hypophysitis**
- **Carotid aneursym**

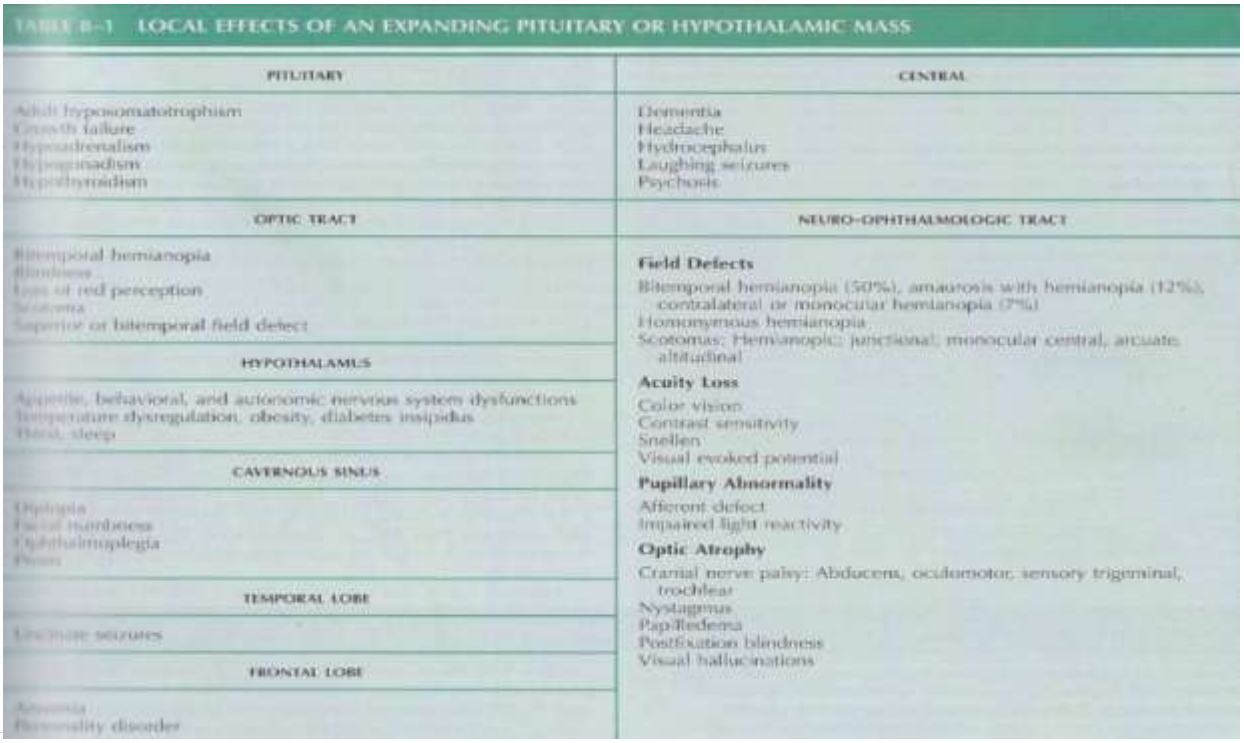
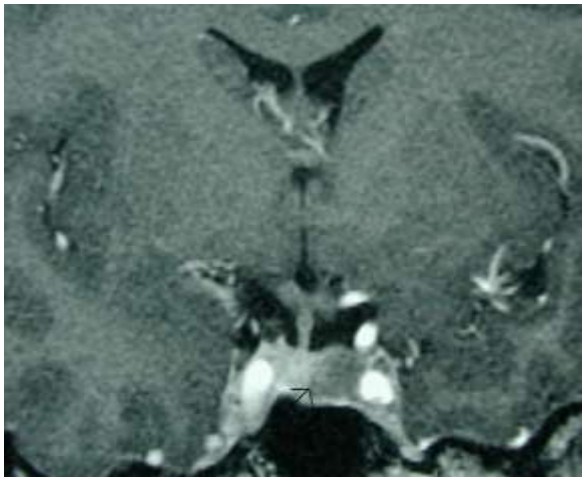
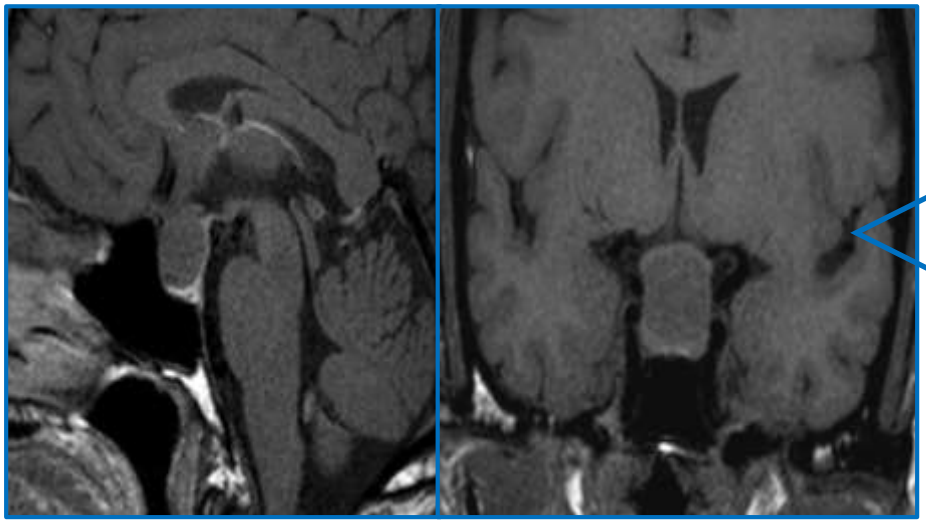


TABLE 8–1 LOCAL EFFECTS OF AN EXPANDING PITUITARY OR HYPOTHALAMIC MASS

PITUITARY	CENTRAL
Adult hyposomatotrophism Growth failure Hypoadrenalism Hypogonadism Hypothyroidism	Dementia Headache Hydrocephalus Laughing seizures Psychosis
OPTIC TRACT	**NEURO-OPHTHALMOLOGIC TRACT**
Bitemporal hemianopia Blindness Loss of red perception Scotoma Superior or bitemporal field defect	**Field Defects** Bitemporal hemianopia (50%), amaurosis with hemianopia (12%), contralateral or monocular hemianopia (7%) Homonymous hemianopia Scotomas: Hemianopic; junctional; monocular central, arcuate, altitudinal **Acuity Loss** Color vision Contrast sensitivity Snellen Visual evoked potential **Pupillary Abnormality** Afferent defect Impaired light reactivity **Optic Atrophy** Cranial nerve palsy: Abducens, oculomotor, sensory trigeminal, trochlear Nystagmus Papilledema Postfixation blindness Visual hallucinations
HYPOTHALAMUS	
Appetite, behavioral, and autonomic nervous system dysfunctions Temperature dysregulation, obesity, diabetes insipidus Thirst, sleep	
CAVERNOUS SINUS	
Diplopia Facial numbness Ophthalmoplegia Ptosis	
TEMPORAL LOBE	
Uncinate seizures	
FRONTAL LOBE	
Anosmia Personality disorder	



Left side microadenoma post contract



Enhanced T1 MRI rathke's cyst / non-enchanced T1 with large rathkes cyst compressing normal pituitary tissue and optic chiasm in the middle of stalk insertion sometimes go suprasellar.

Evaluation of Pituitary Mass:

- Pituitary adenoma: 10 % of all pituitary lesions
- Genetic-related
- MEN-1, Gs-alpha mutation (Guanine nucleatide stimulatory protein gene found in 40 % of somatotroph adenoma/ inactivation mutation in tumor supressing gene in men 1), PTTG gene, FGF receptor-4
- Pituitary incidentaloma: 1.5 -31% in autopsy (prevalence)
  - 10 % by MRI most of them < 1 cm

Functional Adenoma (Hormonal-Secreting)

Non-Functional Adenoma

Non-Functional Pituitary Adenoma NFPA

- Absence of signs and symptoms of hormonal hypersecretion
- 25 % of pituitary tumor
- Needs evaluation either micro or macroadenoma
- Average age 50 – 55 yrs old, more in male

Presentation of NFPA:

- As incidentaloma by imaging
- Symptoms of mass effects (Mechanical pressure)
- Hypopituitarism (mechanism)
- Gonadal hypersecretion

Mass effect tumour expansion lateral compressing cavernous sinus causing cranial nerve palsy like double vision, stretching meninges causing headache, or pushing temporal lobe causing seizure, pushing optic chiasm or headache from apoplexy. Hypopituitarism from suprasellar mass pushing stalk and cutting portal blood supply and hypothalamus signal to pituitary

Treatment:

- Surgery if indicated
  - Recurrence rate 17 % if gross removal, 40 % with residual tumor
  - Predictors of recurrence: young male, cavernous sinus invasion, extent of suprasellar extention of residual tumor, duration of follow up, marker; Ki-67
- Observations with annual follow up for 5 years and then as needed, visual field exam Q 6-12 month if close to optic chiasm. Slow growing tumour
- Adjunctive therapy:
  - Radiation therapy
  - Dopamine agonist
  - Somatostatin analogue

Tumour greater than 2 cm, visual field defect, optic chiasm compression or touching by tumor with no visual field defect, headach, suprasellar/parasellar tumor extension

Table 2
Clinical characteristics of NFPA patients.

	Nomikos et al[15]	Losa et al[16]	Chang et al[17]	Ferrante et al[51]	Total
Number of patients	721	491	663	295	2170
Mean age	54.2 ± 19	–	53 (median)	50.4 ± 14.1	
Gender (M/F)	401/320	276/215	394/269	161/134	1232/938 (56.7% M)
Incidental finding	57 (7.9%)	57 (11.6%)	49 (7.4%)	_	163/1875 (8.7%)
Headaches	70 (9.7%)	–	212 (32%)	122 (41.4%)	404/1679 (24%)
Visual deficits	222 (30.8%)	287/486 (59.1%)	327 (49%)	200 (67.8%)	1036/2170 (47.7%)
Pressure on cranial nerves	_	22 (4.5%)	26 (3.9%)	–	48/1154 (4.2%)
Apoplexy	27 (3.7%)	48 (9.8%)	24 (3.6%)	–	99/1875 (5.3%)
Symptoms of Hypopituitarism	345 (47.8%)	_	342 (51.6%)	118 (40%)	805/1679 (48%)
Documented Hypopituitarism	614 (85%)		–	183 (62%)	797/1016 (78.4%)
Hypogonadism	512/659 (77.7%)	335/474 (70.7%)		128 (43.3%)	975/1261 (77.3%)
Hypoadrenalism	230 (31.9%)	115/478 (24.1%)		77 (26.2%)	422/1494 (28.2%)
Hypothyroidism	129/658 (19.6%)	116/462 (25.1%)		72 (24.5%)	317/1415 (22.4%)
Hyperprolactinemia	199 (27.6%)	251/462 (54.3%)	–	82 (27.6%)	532/1478 (35.9%)

Functional Adenoma

Table 1. Functioning Adenomas: Clinical Disease and Medical Therapy

Clinical disease	Hormone produced by tumor	Estimated frequency (%)	Medical therapy
Acromegaly	Growth hormone	5–10	Somatostatin analog (octreotide) Growth hormone receptor blocker
Cushing's disease	ACTH	10–15	Ketoconazole (blocks cortisol synthesis)
Gonadotroph	FSH, LH	5	None
Prolactinoma	Prolactin	20–30	Dopamine agonist (bromocriptine, cabergoline, pergolide)
Null cell	None	20–25	None
Thyrotropic	TSH	<3	Somatostatin analog (octreotide) Propylthiouracil
Other (including mixed cell adenomas)	None	20	None

ACTH = adrenocorticotropic hormone, FHS = follicle-stimulating hormone, LH = luteinizing hormone, TSH = thyroid-stimulating hormone.

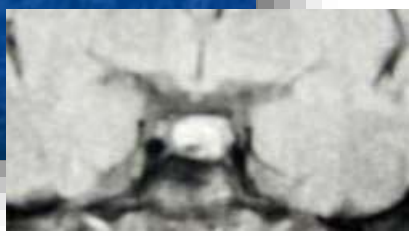
MRI is the imaging study of choice.

All functional adenomas will result in hormonal effects

Prolactinoma

20-30 % of all pituitary tumors

- Most common functional pituitary tumor
- 10% are lactotroph and somatotroph such as GH producing
- Presents with amenorrhea and infertility
- Prolactinomas lose TRH response
- Microadenomas <10mm on MRI
- Macroadenomas >10mm



Signs and symptoms:

Hyperprolactinoma

Amenorrhea, primary Amenorrhea, oligomenorrhea, infirtility, decreased libido, impotence, premature ejaculation, oligospermia, erectile dysfunction, Galactorrhea, osteporosis

Mass effect

Decrease visual aquity, blurred vision, visual feild abnormalitiesm headach, cranial palsies, Hydrocephalus (rare), pituitary apoplexy, hypopituitrism, seizure (temporal lobe), unilateral oxophthalamus (rare)

Management:

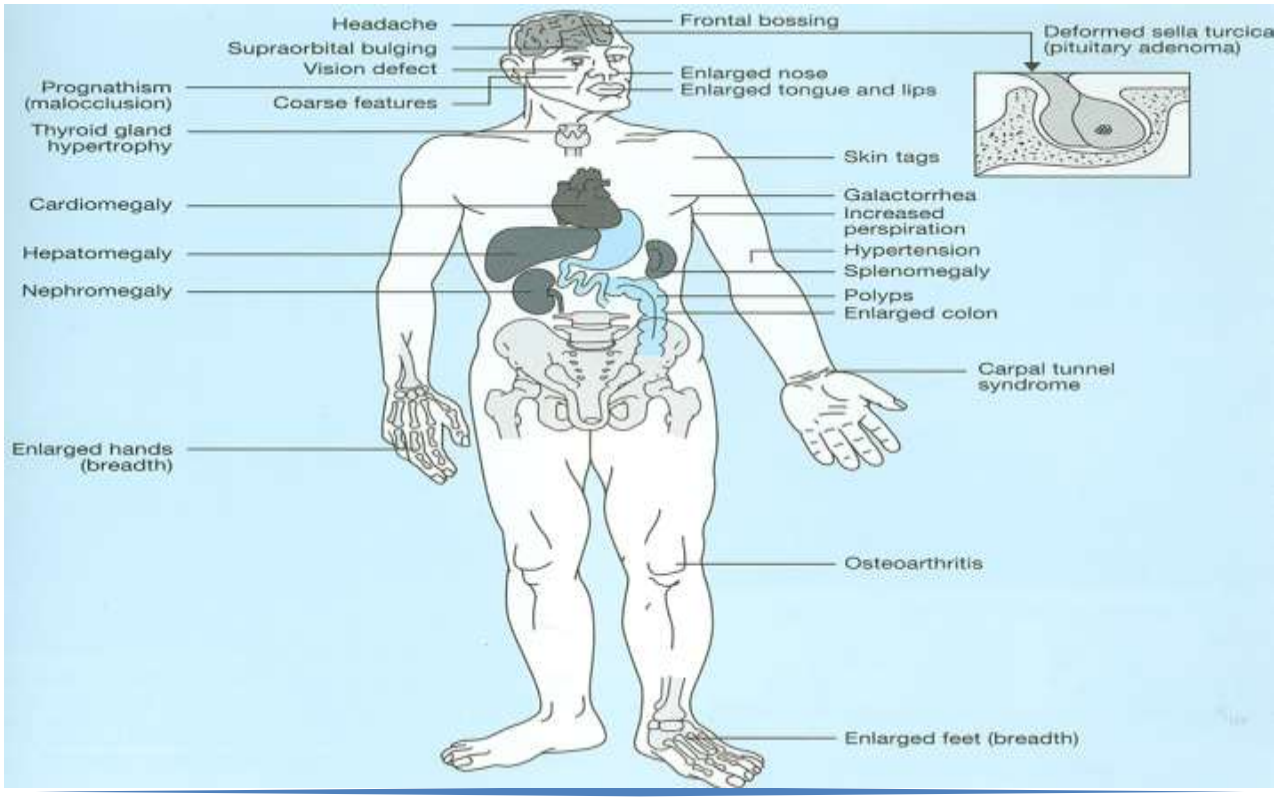
- Diagnosis: High prolactin after excluding other causes
- Management: Dopamine agonist
  - Surgery if no response
  - Radiation therapy

Growth hormone

- Pituitary tumor as mass effect →→ Growth hormone deficiency
- Hyperfunctioning mass →→ Acromegaly

Diagnosis:

- Its deficiency is Diagnosed in children and adult
- GH, IGF-I level
- **Dynamic testing:** clonidine stimulation test, glucagon stimulation, exercise testing, arginine-GHRH, insulin tolerance testing
- **X-ray of hands:** delayed bone age
- **In Adult:** Insulin tolerance testing, MRI pituitary to rule out pituitary adenoma
- **Management:** GH replacement



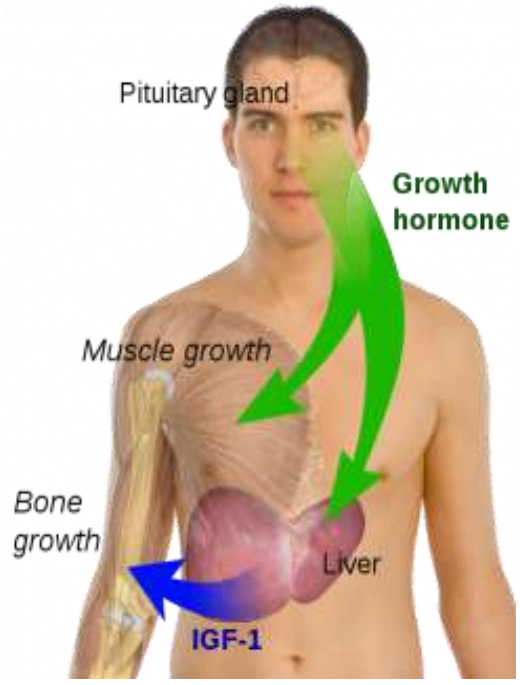
Acromegaly

Table 1. Clinical Features of Acromegaly.

Local tumor effects	**Visceromegaly**
Pituitary enlargement	Tongue
Visual-field defects	Thyroid gland
Cranial-nerve palsy	Salivary glands
Headache	Liver
Somatic systems	Spleen
Acral enlargement, including thickness of soft tissue of hands and feet	Kidney
Musculoskeletal system	Prostate
Gigantism	**Endocrine and metabolic systems**
Prognathism	Reproduction
Jaw malocclusion	Menstrual abnormalities
Arthralgias and arthritis	Galactorrhea
Carpal tunnel syndrome	Decreased libido, impotence, low levels of sex hormone–binding globulin
Acroparesthesia	Multiple endocrine neoplasia type 1
Proximal myopathy	Hyperparathyroidism
Hypertrophy of frontal bones	Pancreatic islet-cell tumors
Skin and gastrointestinal system	Carbohydrate
Hyperhidrosis	Impaired glucose tolerance
Oily texture	Insulin resistance and hyperinsulinemia
Skin tags	Diabetes mellitus
Colon polyps	Lipid
Cardiovascular system	Hypertriglyceridemia
Left ventricular hypertrophy	Mineral
Asymmetric septal hypertrophy	Hypercalciuria, increased levels of 25-hydroxyvitamin D_3
Cardiomyopathy	Urinary hydroxyproline
Hypertension	Electrolyte
Congestive heart failure	Low renin levels
Pulmonary system	Increased aldosterone levels
Sleep disturbances	Thyroid
Sleep apnea (central and obstructive)	Low thyroxine-binding–globulin levels
Narcolepsy	Goiter

Clinical picture and presentation

- GH level (not-reliable, pulsatile)
- IGF-I
- 75 g OGTT tolerance test for GH suppression
- Fasting and random blood sugar, HbA1c
- Lipid profile
- Cardiac disease is a major cause of morbidity and mortality
- 50 % died before age of 50
- HTN in 40%
- LVH in 50%
- Diastolic dysfunction as an early sign of cardiomyopathy
- Headache, Bitemporal hemianopsia, sleep Apnea



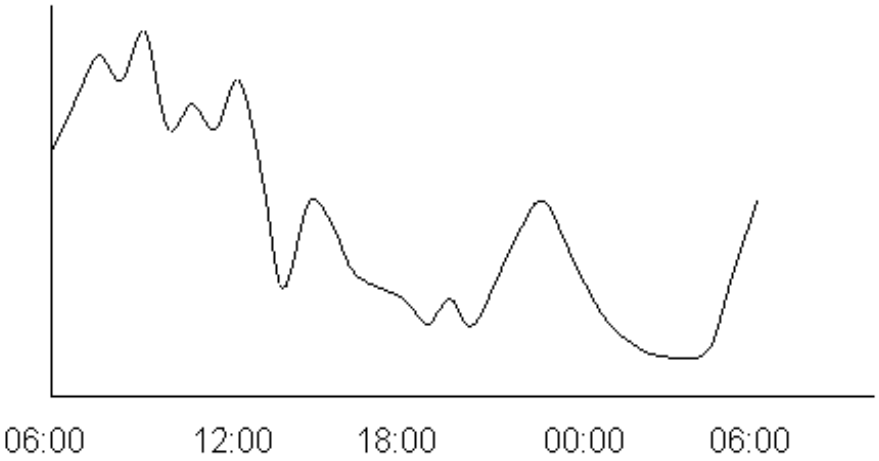
Medical treatment:

- Somatostatin analogue
- Surgical resection of the tumor – Tx of choice

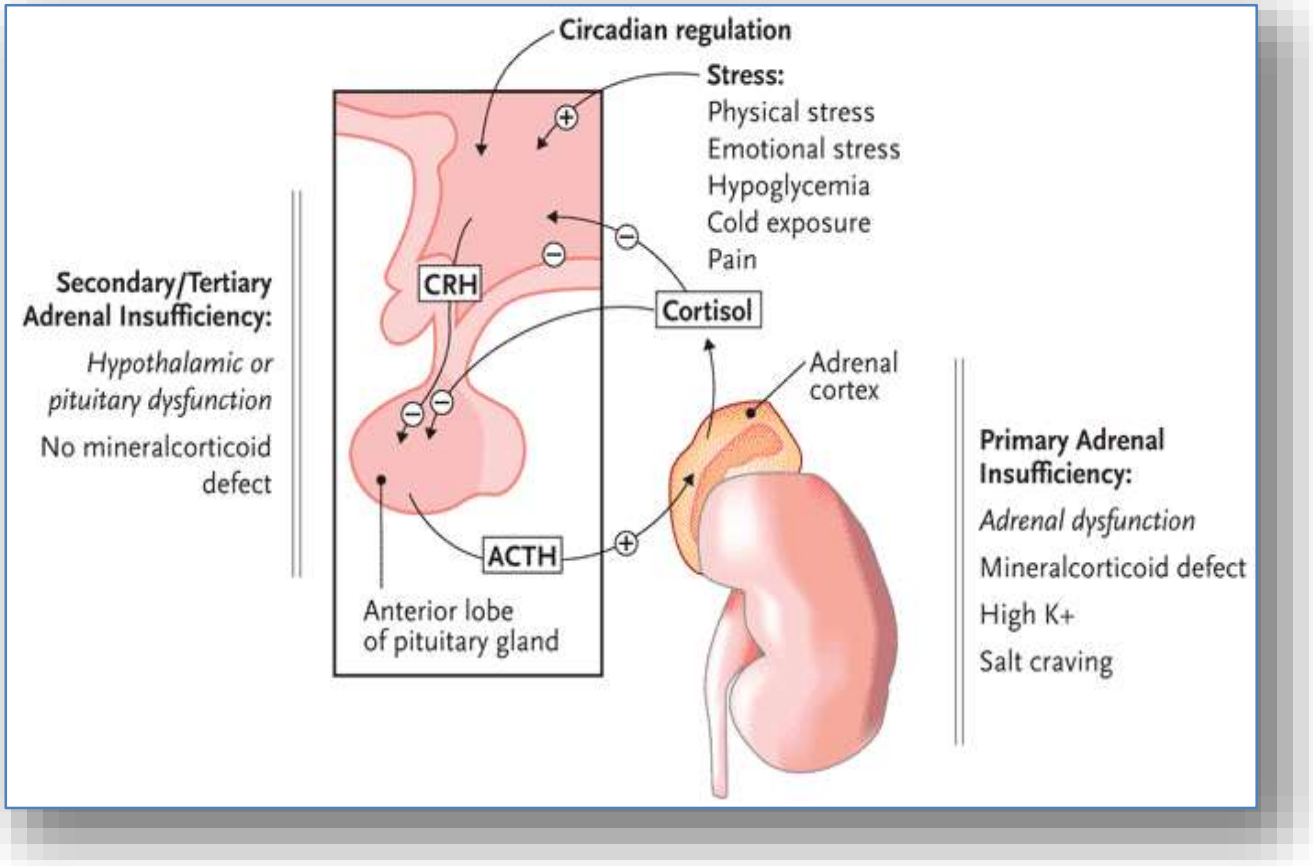
Adrenal Gland:

HPA-axix

- 2nd adrenal insufficiency
- Glucgocorticoid replacement
- Circadian rhythm of cortisol secretion
- Early morning cortisol between 8-9 am



ACTH Disorders



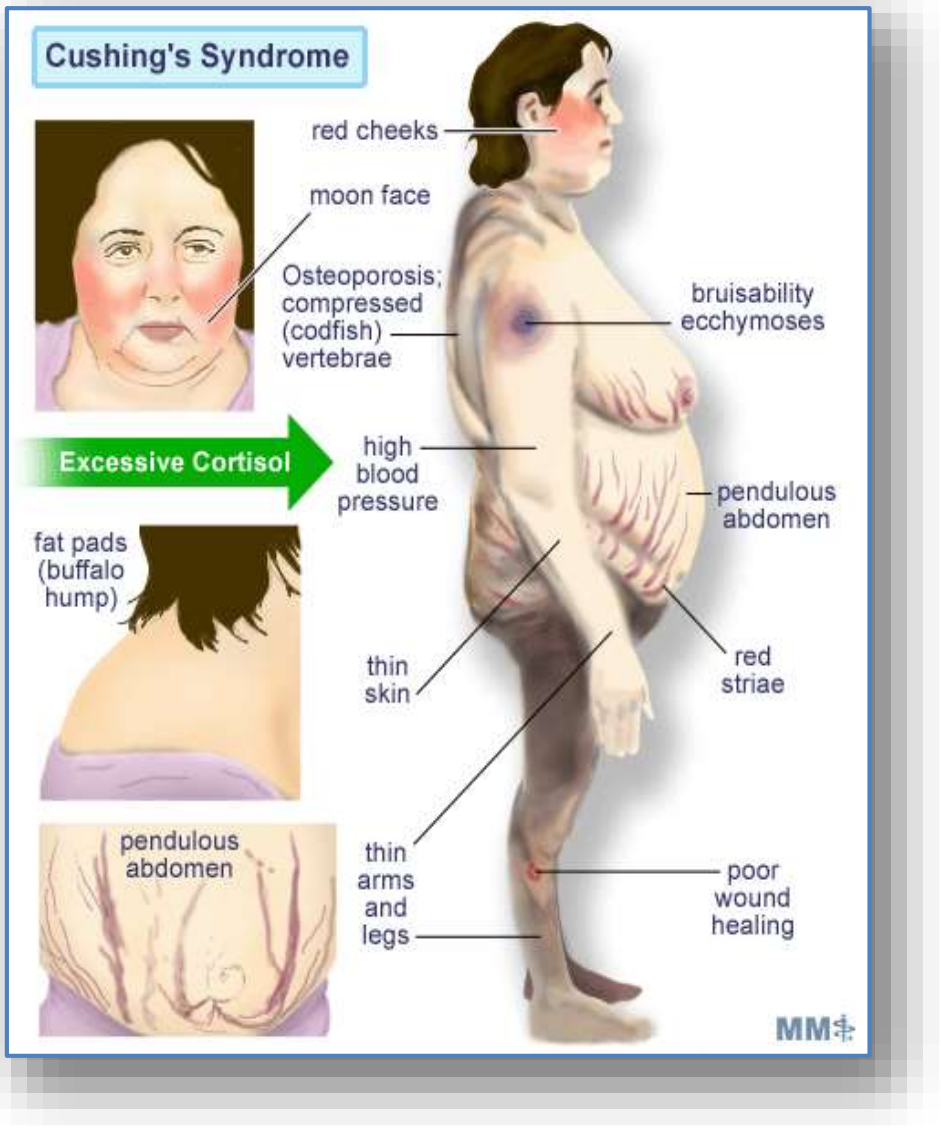
Hypoadrenalism:

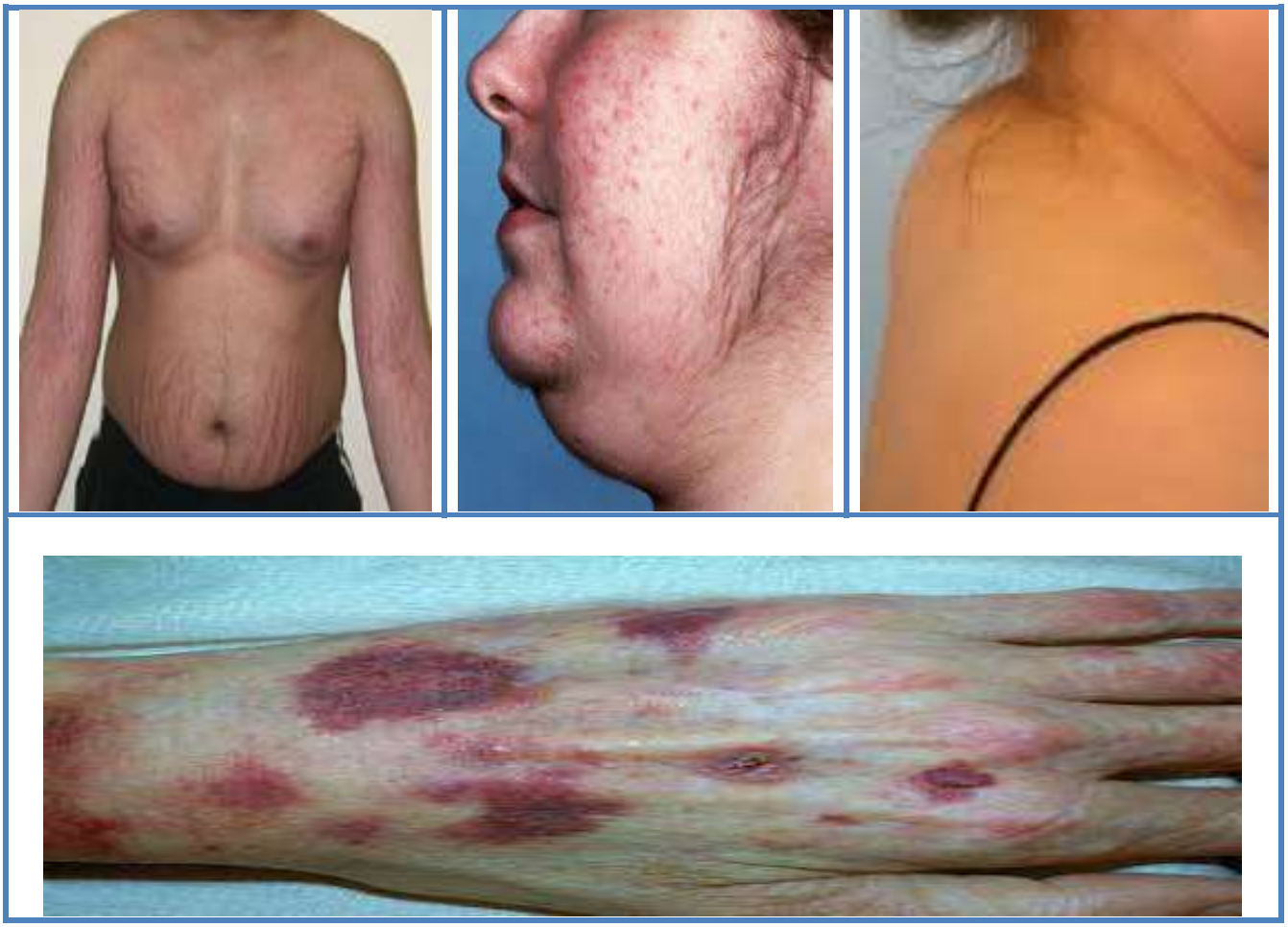
- Nausea
- Vomiting
- Abdominal pain
- Diarrhea
- Muscle ache
- Dizziness and weakness
- Tiredness
- Weight loss
- Hypotension

Diagnosis:

- Low ACTH and Low morning cortisol
- Stimulation test: Insulin tolerance test
- Management: Steroid replacement

Excessive Cortisol (Cushing):





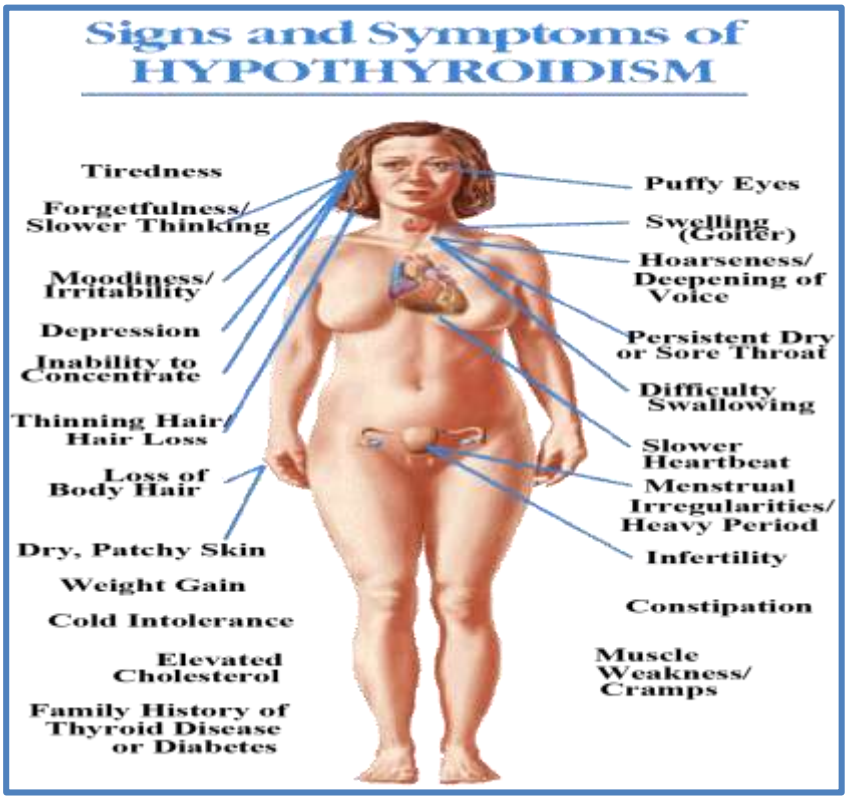
- ♠ 80 % HTN
- ♠ LVH
- ♠ Diastolic dysfunction, intraventricular septal hypertrophy
- ♠ ECG needed: high QRS voltage, inverted T-wave
- ♠ Echocardiogram preop
- ♠ OSA: 33% mild, 18% severe. Needs respiratory assessment and careful use of sedative during surgery
- ♠ Glucose intolerance in 60%, control of hyperglycemia
- ♠ Osteoporosis with vertebral fracture→→ positioning of patient in OR (50 %), 20 % with fracture
- ♠ Thin skin→→ difficult IV cannulation, poor wound healing

Diagnosis:

- 1 mg Dexamethasone suppression test
- 24 hrs urine free cortisol
- Salivary cortisol
- ACTH level

Management:

- Surgical resection of pituitary
- Medical Treatment



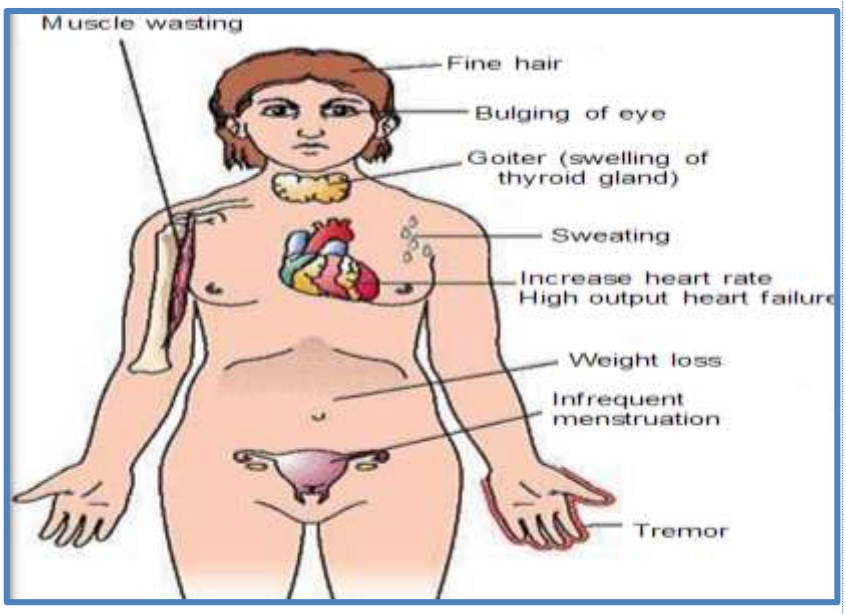
Thyroid Gland: Central

*Hypothyroidism

- Low TSH
- Low free T4 and T3

Management:

- Thyroxin replacement
- Surgical resection of pituitary



*Hyperthyroidism

TSH producing Adenoma:

- Very rare < 2.8 %
- Signs of hyperthyroidism
- High TSH, FT4, FT3
- Treatment preop with anti-thyroid meds pre-op
- Surgical resection of adenoma
- Medical therapy: Somatostatin Analogue

Gonadotroph adenoma vs. ovarian failure in menopause

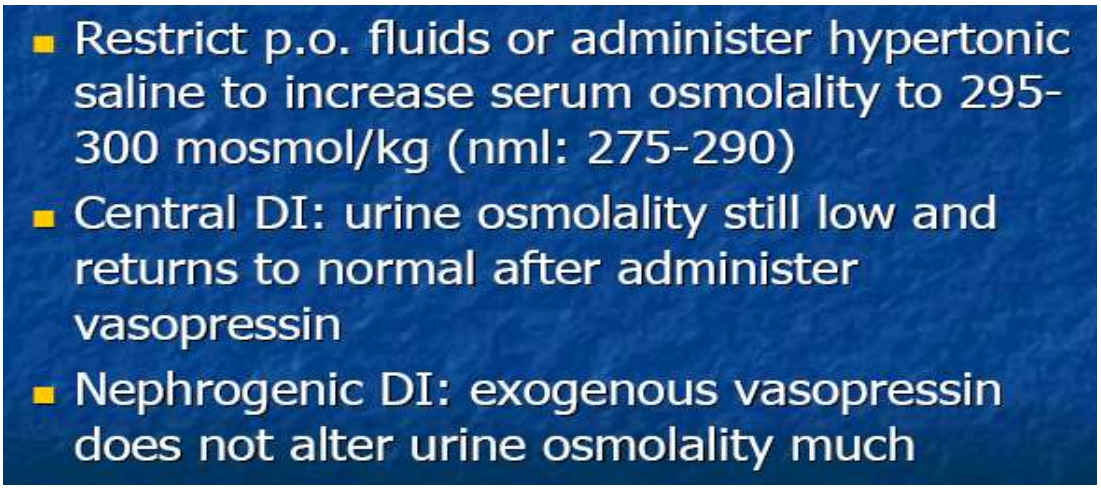
- High TSH, Low LH
- High serum free alpha subunit
- High estridiol, FSH, thickened endometrium and polycystic ovary
- Treatment of non-functioning and gonadotrophin macroadenoma
- Trans-sphenoidal surgery
- +/- Radiation

Central diabetes Inspidus:

- Polydipsia and polyuria 2-15L/day
- Abrupt onset
- Hypernatremia is usually mild unless the patient has problem with thirst drive
    - 30-50% are idiopathic
    - Decreased production by hypothalamus
    - Surgery or trauma
    - Rare with Sheehan's: Mild and undetectable degree

Diagnosis:

- Water deprivation test



Management:

- DDAVP (Desmopressin Acetate)
  - Synthetic analogue
  - Not catabolized by vasopressinase
  - No vasopresor action
  - Intranasally
  - Titrate 10-20ug qd or bid
  - Safe for pregnant and during breastfeeding

Assessment of Pituitary function:

- Baseline: TSH, FT4, FT3, LH, FSH, Prolactin, GH, IGF-I,Testosterone, Estradiol
- MRI brain
- Neuropthalmic evaluation of visual field
- Cardiac and respiratory assessment
- Anesthesiologist for airway and perioperative monitoring
- Neurosurgeon
- ENT for Endonasal evaluation for surgical approach
- Preop hormonal replacement: all pituitary adenoma should be covered with stress dose of HC

SUMMARY

- High levels of prolactin inhibit secretion of GnRH; this leads to decreased secretion of LH & FSH, which in turn leads to decreased production of estrogen and testosterone.
- Parasellar signs and symptoms (mass effects of the tumor) are more prevalent in men than in women. This is largely because the early symptoms in men (e.g., impotence) are often attributed to psychological causes and medical evaluation is delayed, allowing for larger tumor growth.
- Microadenomas (<10 mm diameter) tend to either remain the same size or regress with time. Only 10% to 20% continue to grow.
- Cardiovascular disease is the most common cause of death in patients with acromegaly.
- Laboratory abnormalities in patients with acromegaly:
  - Hyperprolactinemia (tumor secretes prolactin and growth hormone)—30% of patients.
  - Elevations in serum glucose, triglycerides, and phosphate levels.
- Calcification of the suprasellar region seen on brain imaging is nearly diagnostic of craniopharyngioma.
- If a patient presents with polyuria and polydipsia, consider the following first in the differential diagnosis:
  - Diabetes mellitus
  - Diuretic use
  - DI
  - Primary polydipsia
- Primary polydipsia is usually seen in patients with psychiatric disturbances. If the patient is deprived of water, urine osmolarity will increase appropriately.
- In SIADH, volume expansion occurs (due to water retention), but edema is prevented (due to natriuresis).
- Hyponatremia pearls:
  - Hypovolemic hyponatremia —volume contracted
  - Hypervolemic hyponatremia—volume expanded with edema
  - SIADH—volume expanded without edema
- Major characteristics of SIADH:
  - Hyponatremia
  - Volume expansion without edema
  - Natriuresis
  - Hypouricemia and low BUN
  - Normal or reduced serum creatinine level because of dilution
  - Normal thyroid and adrenal function

Questions

1) A 23 year old man complains of persistent headache. He noticed gradual increase in his shoe size over the year. On examination, he has hollow-sounding voice and prognathic jaw. Visual field defect was noted as bitemporal hemianopsia. Wjta is the best initial test?

A. Serum Insulin-like growth factor (IGF-1) and prolactin levels
B. Morning growth hormone level
C. GHRH simulated growth hormone level
D. Lateral skull film to assess Sella-turcica size

2) A 40 years old female complains of weakness, amenorrhea and easily bruising. She has HTN and DM and denied taking drugs other than Metformin and hydrochlorothiazide.
What is the most likely explanation of her symptoms?

A. Pituitary tumor
B. Adrenal tumor
C. Ectopic ACTH production
D. Hypothalamic tumor

2- The process responsible of hypercortisolism is most often caused by ACTH producing Pituitary micro adenoma. Adrenal is next common

Answers:

1st Questions: **a**

2nd Questions: **a**