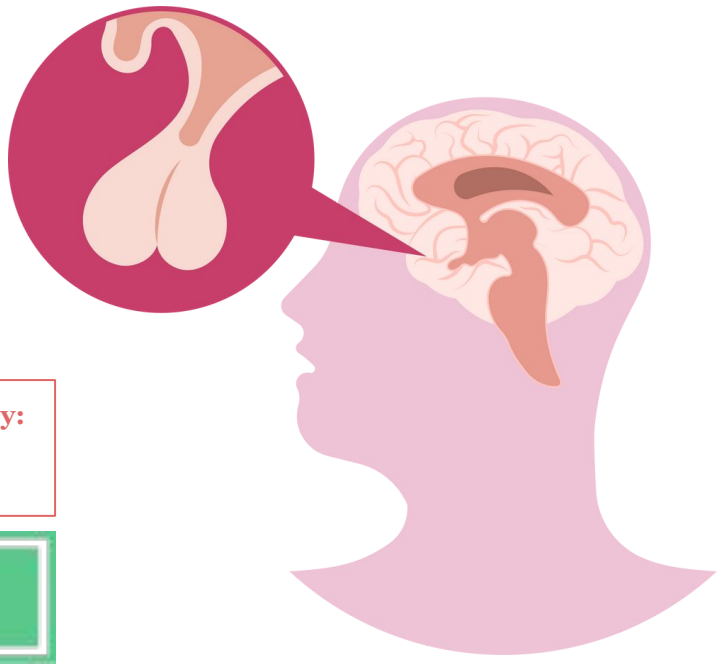
Anterior pituitary disorders



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Editing file

Color index :

Main text (Black)

Female slides (Pink)

Male slides (Blue)

Important things (Red)

Dr's notes (Green)

Extra information (Grey)

OBJECTIVES

To understand basic pathophysiology and feedback for anterior pituitary hormones.

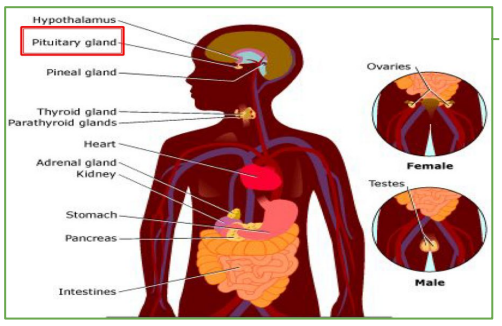
Know about clinical approach for common anterior pituitary gland disorders:

- Common clinical presentations.
- Main laboratory investigations.
- Radiological investigations
- Describe lines of management for each of these conditions.

Pituitary development

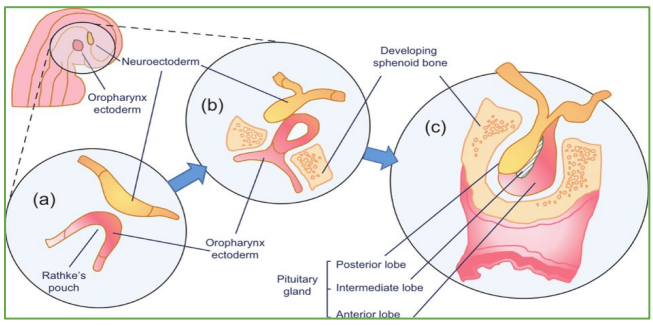
Embryology of Pituitary gland

Anterior pituitary	Posterior pituitary (neurohypophysis)
Rathke's pouch, Ectodermal evagination of oropharynx.	neural cells as an outpouching from the floor of 3rd ventricle.
Synthesis and secrete: (GH,LH,FSH,PRL,TSH,ACTH).	Only storage: Oxytocin, ADH (hypothalamic hormones).
recognizable by 4- 5th wk of gestation and full maturation by 20th week.	
Portion of Rathke's pouch → Intermediate lobe.	
Remnant of Rathke's pouch cell in oral cavity → pharyngeal pituitary.	



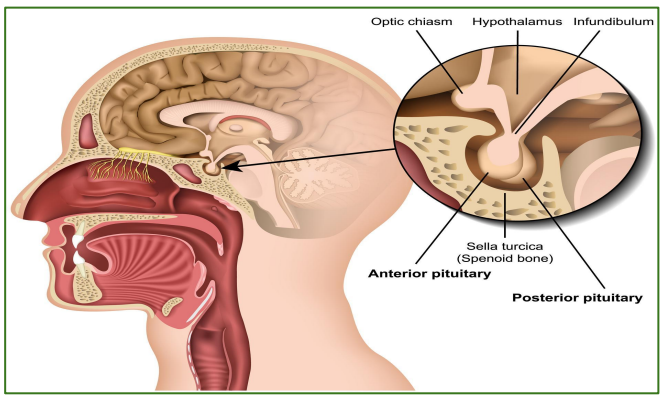
From Dr's slides

Extra for understanding



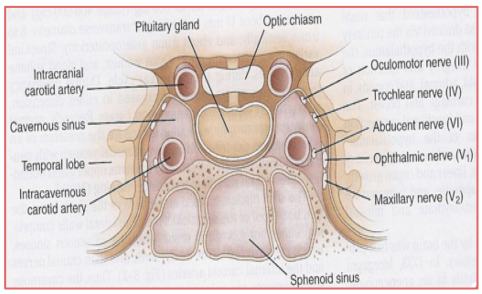
Pituitary disorders

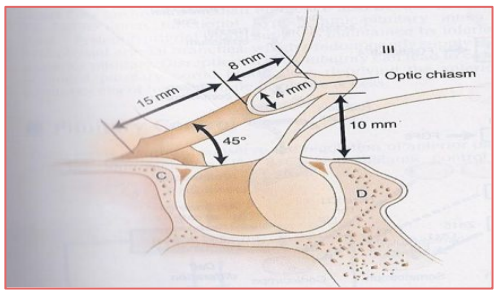
- Anterior pituitary disorders.
- Posterior pituitary disorders
  e.g. Diabetes insipidus. (Not imp)

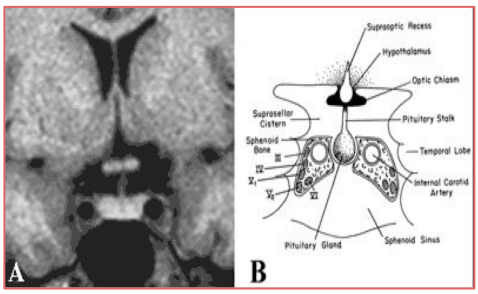


Anatomy overview of pituitary gland

Sella turcica	Pituitary gland is protected by sella turcica which lies at the base of the skull (sphenoid body).
Roof of Sella turcica	Diaphragma sellae (Pituitary stalk and its blood vessels pass through the diaphragm).
Floor of Sella turcica	Sephenoid.
Lateral wall of Sella turcica	1-Cavernous sinus Containing III, IV, VI, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers. 2-Both adjacent to temporal lobes. (Patient with pituitary adenoma may present with ptosis Because the 3rd cranial nerve is affected)
Pituitary stalk	Pituitary stalk in midline joins the pituitary gland with hypothalamus that is below 3rd ventricle.
pituitary cells	Development of pituitary cells is controlled by a set of transcription growth factors like: **Pit-1, Prop-1, Pitx2.**
Pituitary gland measures	It is 15 X 10 X 6 mm, weighs 500 mg but about 1 g in women.
Optic chiasm	lies 10 mm above the gland and anterior to the stalk. (In pituitary adenoma the optic chiasm might be affected and cause visual disturbance)
Blood supply	superior, middle, inferior hypophyseal arteries (internal carotid artery) running in median eminence from hypothalamus.
Venous drainage	to superior and inferior petrosal sinuses to jugular vein.







Pituitary hormones

Anterior (function)

Synthesis and secrete: Go Look For The Adenoma Please.
GH, LH, FSH, TSH, ACTH and **lastly Prolactin**.
A compressive adenoma in pituitary will impair hormone production in this order.

Posterior (function)

Storage only (not synthesis):
because the body of neurons in hypothalamus
1. Oxytocin.
2. ADH(vasopressin).

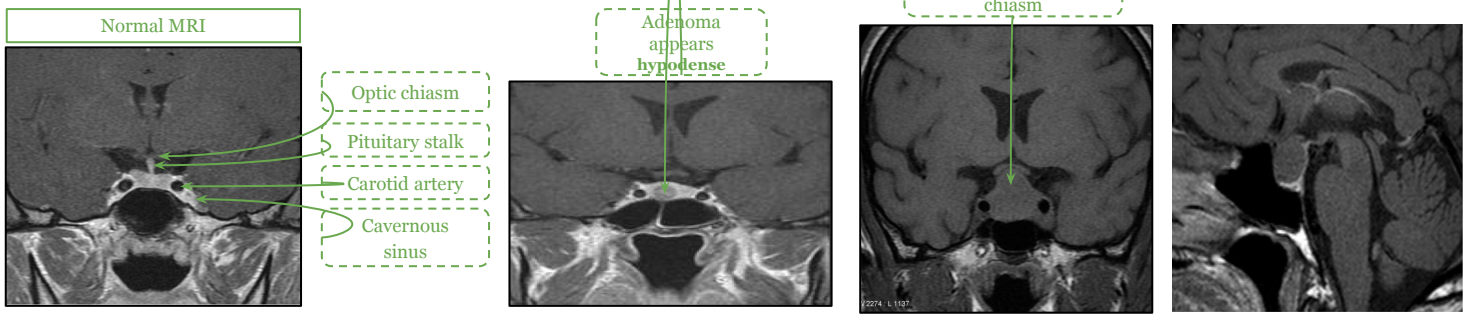
	Somatotrophs	Gonadotrophs	Lactotrophs	Thyrotrophs	Corticotrophs
Stimulators From the hypothalamus	GHRH GHS	GnRH E2 (1)	TRH E2	TRH	CRH AVP gp-130 Cytokines
Inhibitors In case of over secretion we can use the inhibitors as a treatment	IGF-1 Somatostatin Activins	Testosterone E2 Inhibin	Dopamine	T3, T4 Dopamine Somatostatin GH	Steroid
Hormone	**GH** (growth hormone)	LH FSH	PRL (Prolactin)	TSH	ACTH POMC
Target Gland (End organ)	Liver & other tissues	Ovary testes	Breast Other tissues	Thyroid	Adrenals
Target Hormone	IGF-1 (Active form of GH)	testosterone,E2	—	T4	Cortisol
Trophic effects	IGF-1 production Growth induction Insulin antagonism	Sex Steroid Follicular growth Germ cell maturation	Milk production	T4 synthesis and secretion	Steroid production, Androgen

1- E2 Estradiol, is an estrogen steroid hormone and the major female sex hormone. It is involved in the regulation of the estrous and menstrual female reproductive cycles.

If the pituitary gland gets enlarged it will obstruct the 3rd ventricle causing **hydrocephalus**.

And also affect optic chiasm = MACRO Adenoma compressing the optic chiasm = **Bitemporal hemianopia.**

MRI's



4 Anterior pituitary disorders

Functional disorder

Hypersecretion: (GH, LH, FSH, PRL, TSH, ACTH). e.g. Hyperprolactinemia, Acromegaly (↑GH), Cushing's Disease (↑ACTH).
(In females, LH & FSH stimulate ovaries to produce estrogen, In males, they stimulate the testes to produce testosterone)

Hyposecretion: hypopituitarism (isolated, multiple, pan) e.g. Central hypoadrenalism, hypogonadism, hypothyroidism or GH deficiency & Panhypopituitarism. (all the hormones are affected)

Masses (Types):

Functioning = Hypersecretion. (producing certain types of hormones in excessive way)

Non-functioning. (pressure effect causing hypopituitarism (no hormones secreted)

Could be **with/without mass-effect:** Space occupying lesion (compression symptoms, hypopituitarism).

Etiology of pituitary hypothalamic lesions

Non-Functioning Pituitary Adenomas and Pituitary abscess. (benign)

Malignant pituitary tumors: Functional and non-functional pituitary carcinoma.

Lymphocytic hypophysitis.

autoimmune disorder, antibodies attack the pituitary gland which then appears in the MRI scan as adenoma, common in female.

Metastases in the pituitary (breast, lung, stomach, kidney). and infection e.g. TB

Pituitary cysts: Rathke's cleft cyst, Mucoceles, Others.

Carotid aneurysm & Empty sella syndrome.

Carotid aneurysm: the internal carotid enlarges & produces an aneurysm which then enters the pituitary gland that may appear in the MRI scan as adenoma.

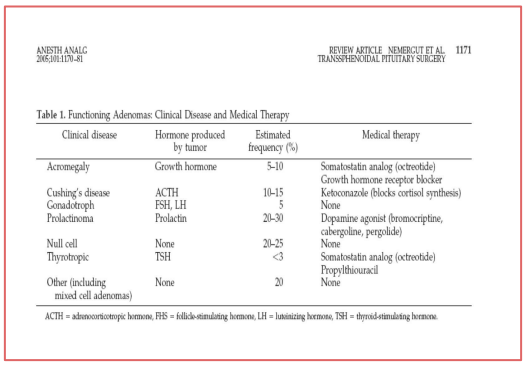
Endocrine active pituitary adenomas: (benign)
1-Prolactinoma (PRL-oma).
2-Somatotropinoma (GH secreting adenoma, Acromegaly).
3-Corticotropinoma (ACTH secreting adenoma, Cushing's disease).
4-Thyrotropinoma (TSH-oma, rare).
5-Other mixed endocrine active adenomas.

Evaluation of pituitary gland

For pituitary Masses

Pituitary incidentaloma	Pituitary adenoma
10% of Normal people may have very small adenomas (< 1 cm in size) which are called Pituitary incidentaloma. They are discovered accidentally in the MRI scan but they **cause no problems.**	The cause of the pituitary adenoma is unknown it might be Genetic.
•1.5-31% in autopsy (prevalence) •10% by MRI most of them <1 cm	• **10 % of all pituitary lesions** • **Genetic-related:** 1. MEN-1 2. Gs-alpha mutation 3. PTTG gene 4. FGF receptor-4

For pituitary Lesions



ANESTH ANALG 2005;101:1170–81 REVIEW ARTICLE NEMERGUT ET AL. 1171
TRANSSPHENOIDAL PITUITARY SURGERY

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.

1. C- clinical (history & examination).
   1-function (oversection or hyposecretion).
   2-Mass (headache, visual symptoms).
   (For evaluation of pituitary lesions we start with a clinical examination)
2. B- biochemical: screening and confirmatory tests.
3. A- Anatomical: MRI of sella turcica & Mass in pituitary.
4. **Treatment:**
   1-surgical, medical, radiation. (most common)
   2-Medical, surgical, radiation.

Pituitary adenomas

Non-functional pituitary adenoma	
C-Clinical	• Asymptomatic **incidentaloma** by imaging • Mass (mechanical pressure, hypopituitarism), visual (bitemporal hemianopia) • Gonadal hypersecretion • Headache & infertility
B-Biochemical (We have to evaluate all the hormones)	• GH, LH, FSH, TSH & ACTH: not high (normal) • Prolactin: low, high, norma (vary)
A-Anatomical	MRI
Treatment	• **Surgery if indicated** • **Observation** • Adjunctive therapy: • 1-Radiation therapy • 2-Dopamine agonist • 3-Somatostatin analogue
functional pituitary adenoma (Prolactinomas most common)	
C-Clinical	• **Oligomenorrhea, amenorrhea or infertility** • **Galactorrhea.** • Mass-effect (mechanical pressure, hypopituitarism) • Sexual dysfunction (in male) • Asleep, stress, pregnancy, lactation and chest wall stimulation or trauma, Renal failure, Liver failure • Medication • On examination: **Visual field defect** (Bitemporal hemianopia) and **Nipple discharge.** • prolactin may increase in level because of stress (it may increase for other reasons not only adenoma)
B-Biochemical	GH, LH, FSH, TSH, ACTH: normal or low **PRL: High** TSH: to rule out Primary Hypothyroidism IGF-1: to rule out acromegaly with co-secretion of prolactin
A-Anatomical	MRI
Treatment	• **Medical-medical-medical (Dopamine agonist) (even if there is bitemporal hemianopia).** **(it is the only high hormone we can treat with medical medical medical).** • Surgical- Radiation (last option)

Y. Greenman, N. Stern / Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 625–638 627

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%)

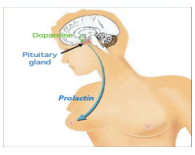
Prolactinomas

- Prolactinoma (high prolactin + Mass)
- Most common of functional pituitary adenoma, 25-30% of all pituitary adenoma.
- Some growth hormone (GH)–producing tumors also co-secrete PRL.
- Prolactinomas in **women**:
  - 90% present with **microprolactinomas**
- Prolactinomas in **men**:
  - 60% present with **macroprolactinomas**

(Most women present with microprolactinomas because they have a clear sign (amenorrhea) and go early, unlike men they don't have a clear sign so they present with macroprolactinomas
Microadenoma is less than 1 cm and macroadenoma is more than 1 cm)

Prolactin low

- **No clinical significant** if there is no mass invading the hypothalamus.
- N.B.: PRL is the only pituitary hormone that is inhibited by hypothalamus.



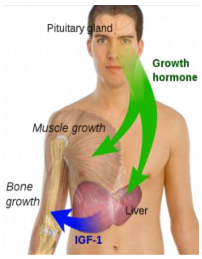
Growth hormone disorders

GH deficiency↓↓

Characteristics:

- Isolated, panhypopituitarism
- Pituitary tumor as mass effect → Growth hormone deficiency
- Diagnosis in children and adult
- Disease in:

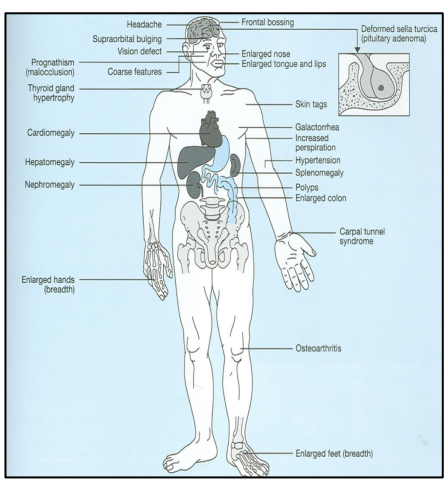
- **Children**: Short stature
- **Adult**: metabolic syndrome (obesity, DM & HTN)

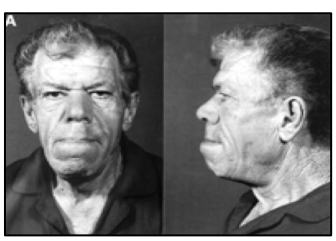


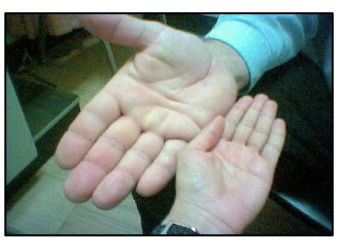
GH deficiency in **children** will cause **short** stature, in **adult** it will cause **decrease** in the **fat breakdown** and **maldistribution** (more fat in the abdomen) **and decrease** the **bone density** causing osteoporosis

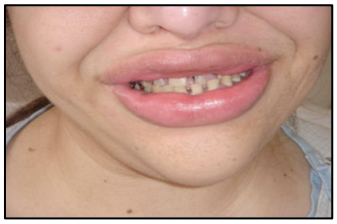
Growth hormone deficiency	
C-Clinical	• **Function: Short stature** • **Mass-effect (mechanical pressure, hypopituitarism)**
B-Biochemical	• Pituitary Function (LH, FSH. PRL, TSH, ACTH, cortisol, testosterone & T4) • Screen: IGF-1 30 (in diagnosis of GH deficiency we measure the IGF-1 because it's stable and produced from the liver) • Dynamic testing: clonidine stimulation test, glucagon stimulation, exercise testing, arginine-GHRH, **insulin tolerance testing**
A-Anatomical	• X-ray of hands: delayed bone age • MRI
Treatment	• GH replacement (Mostly children)

Acromegaly ↑↑









Growth hormone disorders

Acromegaly

C-Clinical	• **Function: Sweating, Enlargement (acral, face gross features, heart, tongue, Jaw, gigantism in children), Galactorrhea** • Mass-effect (mechanical pressure, hypopituitarism) • HTN, CHE, Obstructive sleep apnoea & constipation • On examination: Visual field defect (Bitemporal hemianopia) • Gross features of **Acromegaly**
B-Biochemical	• Pituitary Function (LH,FSH.PRL, TSH, ACTH, cortisol, testosterone, T4) • Screen: **IGF-1 (high)** • Confirmatory Test: 75 g oral glucose tolerance test **(OGTT)** for GH Suppression • Lipid profile • Fasting & random blood sugar, HBA1C
A-Anatomical	• MRI • Echo: Cardiac disease is a major cause of morbidity and mortality 50 % died before age of 50. HTN in 40%, left ventricular hypertrophy **(LVH)** in 50%, Diastolic dysfunction as an early sign of cardiomyopathy
Treatment	**Surgical - Medical** (Somatostatin analogue)- **Radiation**

These two table are the same

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

Extra for understanding

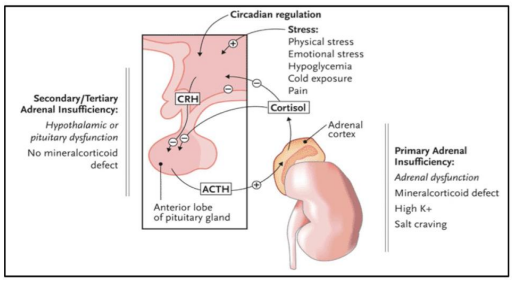
From Dr's slides

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

Cortisol disorders

ACTH disorder

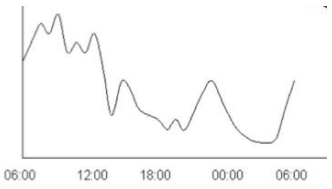


HPA-axis

Circadian rhythm of cortisol secretion:

- Early morning cortisol between 8-9am

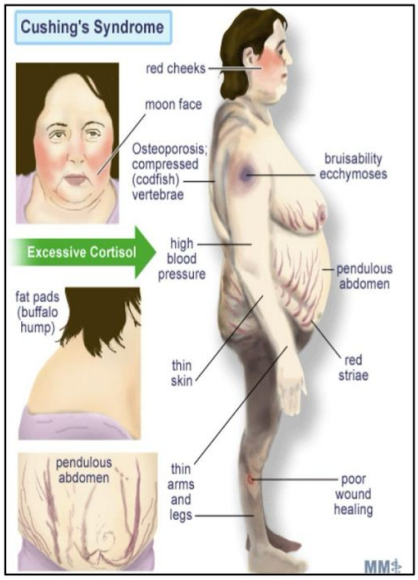
Normally the highest secretion of cortical is in the morning, people with Cushing syndrome will have overproduction of cortisol all the time (loss of circadian rhythm)



Low cortisol (Hypoadrenalism)	
Clinical features	• Nausea, Vomiting, abdominal pain, Diarrhea. • Dizziness and weakness, Tiredness, Muscle ache. • Hypotension & Weight loss
Management	Cortisol replacement
Excessive cortisol (Cushing syndrome)	
C-Clinical	• Function: easily bruising, DM, HTN, irregular period, proximal weakness, recurrent infections, depression • On examination: hirsutism, acne, moon face, central obesity, stria, proximal weakness, supraclavicular fat pad (buffalo hump)
B-Biochemical	• High cortisol, high ACTH. • Confirmatory tests: 24h for urine free cortisol (UFC) • 1Mg DST (dexamethasone suppression test) • Midnight salivary cortisol (one of the diagnosis method for Cushing syndrome is measuring the cortisol level at night)
A-Anatomical	MRI
Treatment	Surgical - Medical - Radiation

Low cortisol: Hypoadrenalism
↓ACTH,↓cortisol→ adrenal insufficiency→ hypotension, weight loss, nausea, vomiting, diarrhea and the patient might die in case of stress because it is a stress hormone which is important during stress.

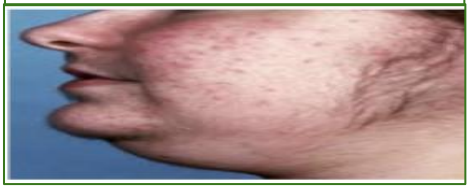
High cortisol
ACTH adenoma →Cushing
↑ACTH ↑cortisol →Cushing→ loss of collagen→ The vessels will be visible.



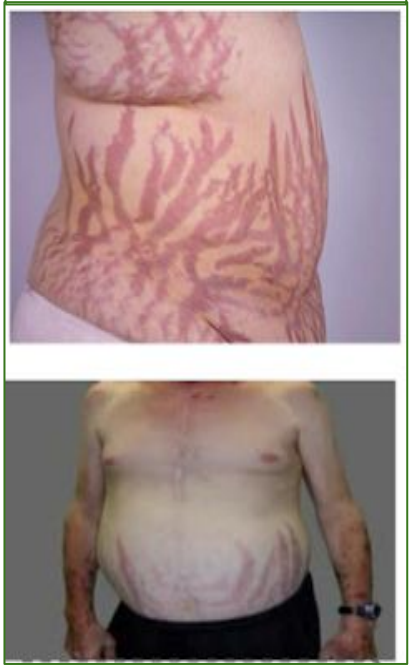
Cortisol disorders

Red striae (ACTH adenoma)

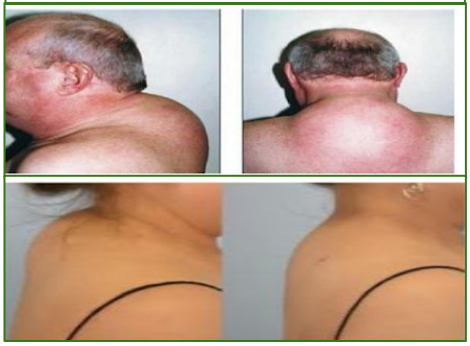
Hirsutism in women (cushing's syndrome)



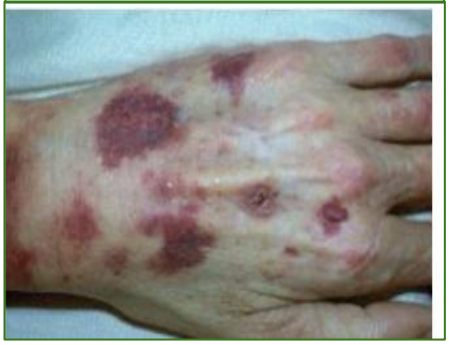
striae purple, wider >1cm (cushing's syndrome)



Buffalo hump (cushing's syndrome)



ecchymosis (cushing's syndrome)



HPA-axis (excessive cortisol):

1

80 % HTN .

2

ECG needed: high QRS voltage, inverted T-wave.

3

OSA: 33% mild, 18% severe. Needs respiratory assessment and careful use of sedative during surgery.

4

Diastolic dysfunction, interventricular septal hypertrophy.

5

Echocardiogram preop.

6

Osteoporosis with vertebral fracture→→ positioning of patient in OR (50 %), 20 % with fracture.

7

Left ventricular hypertrophy.

8

Glucose intolerance in 60%, control of hyperglycemia.

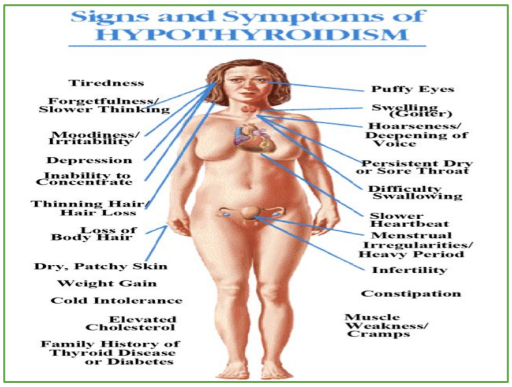
9

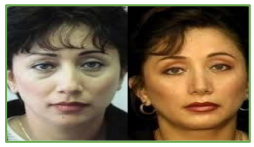
Thin skin→ difficult IV cannulation, poor wound healing, Red stria.

Thyroid disorders

Definition (extra for better understanding):
central hypothyroidism refers to thyroid hormone deficiency due to a disorder of the pituitary, hypothalamus or hypothalamic-pituitary portal circulation, resulting in diminished thyroid-stimulating hormone(TSH), thyrotropin-releasing hormone(TRH) or both. (team438)

Central hypothyroidism	
C-Clinical	• Function: fatigue, weight gain, irregular menses, dry skin, depression, cold intolerance, increase sleep, slow thinking, bad memory. • On examination: obesity, depressed face & eyebrow.
B-Biochemical	• Low TSH • Low T3 & T4
A-Anatomical	MRI
Treatment	• Thyroxine replacement • Surgical removal of pituitary adenoma if large • radiation

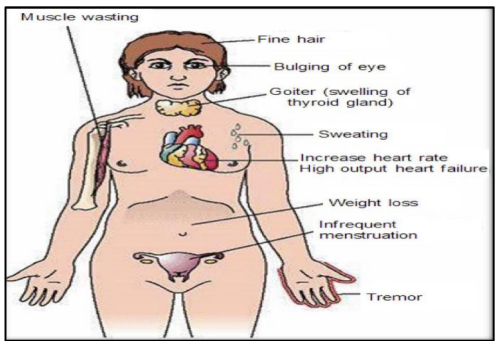




Types of hypothyroidism:
1-primary hypothyroidism: failure of thyroid gland → elevated TSH → deficiency of thyroid hormone.
2-secondary hypothyroidism: failure of pituitary to secrete TSH, failure of the hypothalamic pituitary axis → deficiency of thyroid hormone.

Definition (extra for better understanding):
TSH-secreting pituitary adenomas are benign tumours of the pituitary gland. They produce too much thyroid stimulating hormone (TSH), which causes the thyroid gland to enlarge and produce thyroid hormone in excess, leading to un overactive thyroid (hyperthyroidism). (team438)

TSH-producing adenoma	
C-Clinical	• Very rare < 2.8% • Signs of hyperthyroidism.
B-Biochemical	• High TSH FT3 & FT4
A-Anatomical	MRI
Treatment	• Treatment preoperative with anti-thyroid meds. • Surgical resection of adenoma. • Medical therapy: somatostatin analogue.



Thyroid disorders

High FSH with Low LH, High serum free alpha subunit.

Thickened endometrium and polycystic ovaries, high estridiol and FSH.

Gonadotroph adenoma: 1-Surgical resection (if large). 2-Radiation therapy.

Gonadotroph adenoma VS menopause and ovarian failure

Assessment of pituitary function:

01 Baseline: TSH,FT4,LH,FSH, (Testosterone or Estradiol),Prolactin, GH, IGF-1, ACTH, cortisol and electrolyte

02 Brain MRI, Neurophthalmic evaluation of visual field

03 Cardiac and respiratory assessment

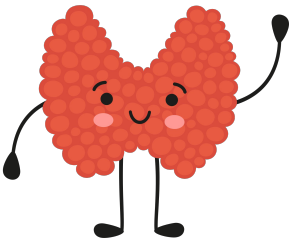
04 Anesthesiologist for airway and perioperative monitoring

05 Neurosurgeon, ENT for Endonasal evaluation for surgical approach

06 Preop hormonal replacement: Maybe need to be covered with stress does of HC **(Hydrocortisone)**

If patient present with pituitary adenoma, first thing to do is take history, 2nd is to evaluate hormones then MRI, then decide the treatment.

Most of them surgical is the 1st line of treatment except high secretion of prolactin medical is the 1st line of treatment.



MCQs

Q1

Which one of the following is a major cause of morbidity and mortality in patients with acromegaly?

- A- liver diseases.
- B- Renal diseases.
- C- Cardiac diseases.
- D- Bone fractures.

Q2

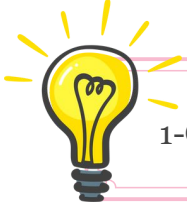
A 45 year old man presented with 2 years history of increase in size of his hands & feet. His friends noticed a change in his facial feature & spacing of his teeth. What is the most likely diagnosis?

- A- ACTH secreting adenoma.
- B- Growth hormone secreting adenoma.
- C- Prolactin secreting adenoma.
- D- TSH secreting adenoma.

Q3

A 50 year old man has a history of hypertension and diabetes. Laboratory test showed high IGF-1 and on MRI there was pituitary macroadenoma. What is the next step in management?

- A- Surgery.
- B- Somatostatin antagonist.
- C- Dopamine agonist.
- D- Radiation therapy.



1-C 2-B 3-A

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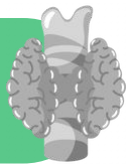
يزن الأحمري

Leader

رغد المصلح

Member

عبدالله الضويحي



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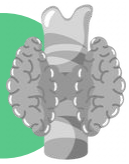

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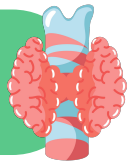

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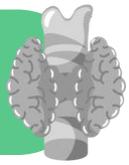
ريوف الأحمري



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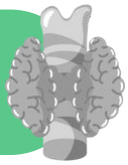

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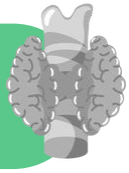

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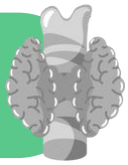

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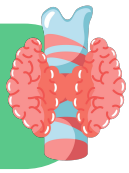

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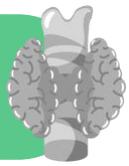

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