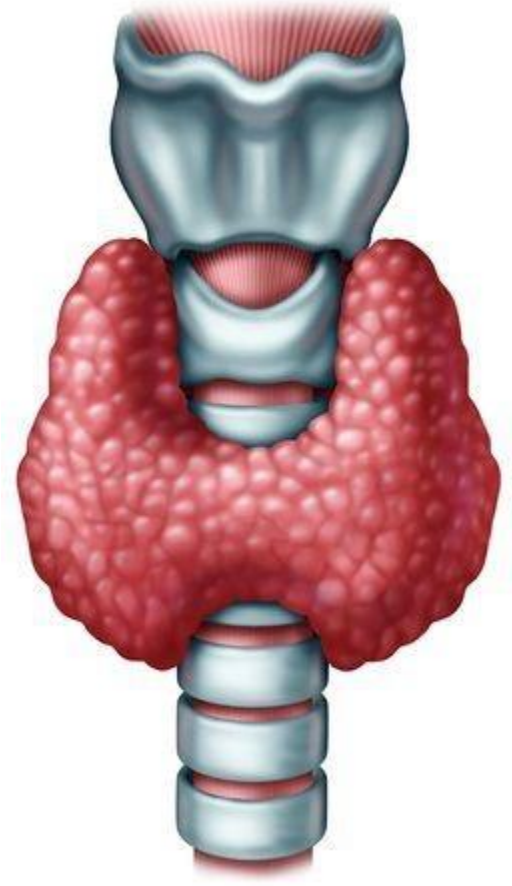

Anterior Pituitary Disorders

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.

Revised By
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Color index:

- Important
- Notes
- Extra

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Waiting for your Feedback

Reference: Girls' & Boys' Slides

Pituitary Development

Anterior Pituitary:

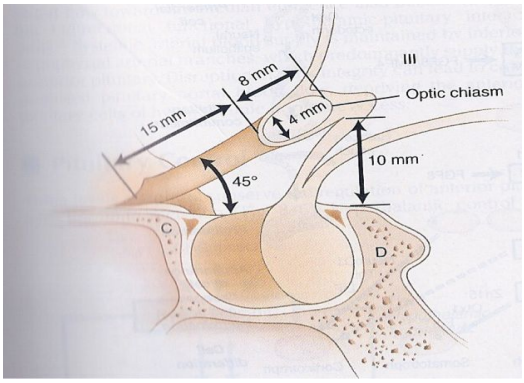
- Rathke's pouch, ectodermal evagination of <u>oropharynx</u>.
- Synthesis and secretes (GH, LH, FSH, PRL, TSH, ACTH).
  - ✓ Recognizable by 4–5th week of gestation* and full maturation by 20th week.
  - ✓ Portion of Rathke's pouch –> intermediate lobe
  - ✓ Remnant of Rathke's pouch cell in oral cavity –> pharyngeal pituitary.

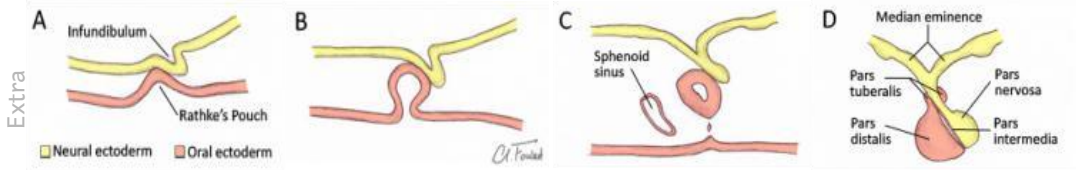
*The process or period of developing inside the womb.

Posterior pituitary (neurohypophysis):

- <u>Neural cells</u> as an outpouching from the floor of 3rd ventricle.
- ONLY storage: oxytocin, ADH (hypothalamic hormones).

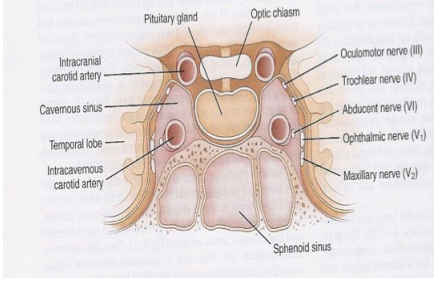
- Pituitary stalk in midline joins the pituitary gland with hypothalamus that is below 3rd ventricle. Normal pituitary stalk length 5– 7 mm , 2–3 mm in diameter
- Development of pituitary cells is controlled by a set of **transcription growth factors** like (Pit–1, Prop–1, Pitx2).





Sella Turcica

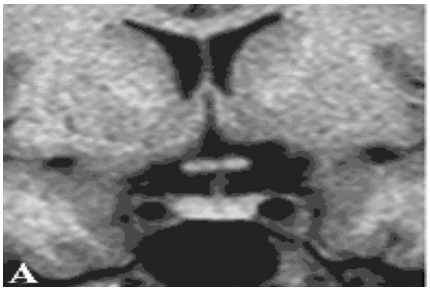
- Lies at the base of the skull.
- Roof: diaphragma sellae. is formed by a reflection of dura mater preventing CSF from entering the sella turcica by this diaphragm.
  - ✓ Pituitary stalk and it's blood vessels pass through the diaphragm.
- Floor: sphenoid sinus.
- Lateral walls: cavernous sinus:
  - ✓ Containing III, IV, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers.
  - ✓ Both adjacent to temporal lobes. Any pressure on it, will lead to seizures.

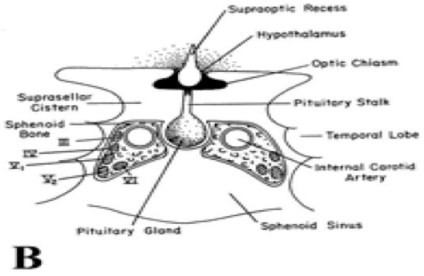


Pituitary Gland

- Pituitary gland measures: 15x10x6 mm, weighs 500 mg but about 1g in women
- Optic chiasm:
  - ✓ Lies 10 mm above the gland anterior to the stalk
- 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

Normal pituitary anatomy





Pituitary function

Anterior pituitary hormones

- **G**o **L**ook **F**or **T**he **A**denoma **P**lease
- **G**H, **L**H, **F**SH, **T**SH, **A**CTH, **P**rolactin
- A compressive adenoma in pituitary will impair hormone production in this order

Posterior pituitary hormones

- Oxytocin
- ADH (vasopressin)
- REMEMBER storage not synthesis

Anterior pituitary Function: this schedule is **summarizing** all anterior pituitary hormones that we've took it in **physiology**

	Somatotroph	Gonadotroph	Lactotroph	Thyrotroph	Corticotroph
Stimulator	GHRH + GHS	GnRH + E2	TRH + E2	TRH	CRH, AVP, gp-130 ,cytokines
Inhibitor	IGF-F, Activins Somatostatine	Testosterone, E2, Inhibin		T3 , T4, Dopamine, GH, Somatostatin	Steroid
Hormone	GH	LH , FSH	PRL	TSH	ACTH, POMC
Target gland	Liver and other tissues	Ovary and testes	Breast + other tissue	Thyroid	Adrenals
Target hormon	IGF-1	Testosterone + E2		T4	Cortisol
Trophic effect	IGF-1 production, Growth induction, insulin antagonism	Sex steroid Follicular growth Germ cell maturation	Milk production	T4 syntheses and secretion	Steroid production Androgen

Start by asking about mass effects, then functional effects

Pituitary Disorders

Pituitary Disorders

- anterior pituitary disorders
  - function:
    - hypersecretion: (GH, LH, FSH, PRL, TSH, ACTH)
    - hyposecretion: hypopituitarism (isolated, multiple, pan)
  - masses:
    - functioning = hypersecretion
    - non-functioning
    - with or without mass-effect:
      - ✓ space occupying lesion (compression symptoms, hypopituitarism)
- posterior pituitary disorders
  - diabetes insipidus

Etiology of pituitary-hypothalamic lesions

- Non-functioning pituitary adenomas
- Endocrine active pituitary adenomas
  - Prolactinoma (PRL-oma)
  - Somatotropinoma (GH secreting, acromegaly)
  - Corticotropinoma (ACTH secreting adenoma, cushing's disease)
  - Thyrotropinoma (TSH-oma, rare)
  - Other mixed endocrine active adenomas
- Malignant pituitary tumors
  - Functional and non-functional pituitary carcinoma
- Metastasis in the pituitary (breast, lung, stomach, kidney) these are the most common
- Pituitary cysts
  - Rathke's cleft cyst, mucoceles, others
- Empty sella syndrome CSF is found in sella, leads to partial or complete atrophy of the pituitary
- Pituitary abscess e.g. TB
- Lymphocytic hypophysitis auto-immune
- Carotid aneurysm

Evaluation of Pituitary Disorders

Evaluation of Pituitary mass

- Pituitary adenoma: very common
  - 10% of all pituitary lesions
  - Genetic-related
    - MEN-1, Gs-alpha mutation, PTTG gene, FGF receptor-4
- Pituitary incidentaloma: headache, small adenoma without symptoms.
  - prevalence: 1.5 -31% in autopsy.
  - 10% by MRI most of them <1 cm

Evaluation of Pituitary lesion

To evaluate any pituitary lesions we start in this order:
Clinical, Biochemical then Anatomical. **CBA**

C: Clinical	**History and Examination** o function (oversection or hyposecretion) o Mass (headache, visual symptoms and seizures)
B: Biochemical	o Screen Test IGF-1 for GH o Confirmatory Test
A: Anatomical	MRI of sella turcica MRI is the bests way to assess pituitary Gland
Treatment	It is either Surgical – Medical – Radiation In most cases or Medical – Surgical – Radiation

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.

ACTH "Cortisol" is the most Important hormone, and is last hormone that will be missed.
GH is the least important.

Prolactinoma is the most common disease.

Disorders of Pituitary Function

- Hypopituitarism:
  - Central hypoadrenalism, hypogonadism, hypothyroidism or GH deficiency.
  - Panhypopituitarism.
- Hypersecretion of Pituitary Hormones:
  - Hyperprolactinemia
  - Acromegaly
  - Cushing's Disease

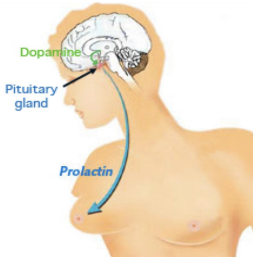
Non- functional pituitary adenoma Normal or low secretions

C: Clinical	**Asymptomatic** , incidentaloma by imaging. Mass-effect : mechanical pressure, hypopituitarism, Headache visual (bitemporal hemianopia) Gonadal hypersecretion.
B: Biochemical	GH,LH,FSH,TSH,ACTH: not high Will be low if the mass is compressing PRL : low ,high, normal Remember: Always test for all hormone parameters
A: Anatomical	MRI
Treatment	Surgery if indicated For larger masses Observation Adjunctive therapy: o Radiation therapy o Dopamine agonist o Somatostatin analogue.

Functional Pituitary mass: 1. Prolactin Disorders

1. Low prolactin

No clinical significant if there is no mass invading the hypothalamus.



N.B. : PRL is the only pituitary hormone that is inhibited by hypothalamus.

2. High prolactin (Prolactinoma)

Most common of functional pituitary adenomas, 25–30% of all pituitary adenomas.
Some growth hormone (GH)–producing tumors also co–secrete PRL.
Prolactinomas **women**:

90% present with **micro**prolactinomas Because it disturbs the menstrual cycle So females present early.

Prolactinomas in **men** :

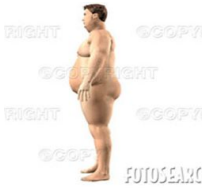
60% present with **macro**prolactinomas

Evaluation of Prolactinoma:

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. –O/E: Visual field defect (Bitemporal hemianopia). –Nipple discharge.
B: Biochemical	GH,LH,FSH,TSH,ACTH: normal or low PRL : High TSH: R/O Hypothyroidism(primary) IGF–1: R/O* acromegaly co–secretion *R/O rule out
A: Anatomical	MRI
Treatment	Treatment: **Medical – Medical – Medical (Dopamine agonist)**, Surgical– Radiation. It is very important to known that only prolactinoma is treated medically as first line of treatment

Functional Pituitary mass: 2. Growth hormone disorders

03:14 1. growth hormone deficiency



- Isolated, panhypopituitarism
- Pituitary tumor as mass effect ⟶ Growth hormone deficiency
- diagnosis of disease in:
  - Children: Short stature We treat it with GH supplementation
  - Adult: metabolic syndrome, weight gain and social isolation.

Evaluation of GH deficiency:

C: Clinical	Function : Short stature No significant function effects in adults Mass-effect (mechanical pressure, hypopituitarism)
B: Biochemical	Pituitary Function (LH,FSH.PRL, TSH, ACTH, cortisol, T4, testosterone) Screen: IGF-1 Dynamic testing (diagnostic or confirmatory tests): - clonidine stimulation test glucagon stimulation - exercise testing, - arginine-GHRH - insulin tolerance testing*
A: Anatomical	X-ray of hands: delayed bone age (e.g. if the patient is 15 years old but his/her x-ray shows bones of 10 years old) MRI
Treatment	Gh replacement it is much more important for pediatric patients, it can help socially isolated adult patients.

*As we know if growth hormone high glucose level will be low, and vice versa.
We can't mussre GH directly because it is palstile.
So, if we suspect that this patient has GH deficiency,logically glucose level is high.
We give the patient insulin to decrease glucose level, blood samples were taken at 0, 30, 45, 60, and 90 min. And we compare GH level and Glucose level in these samples.
So normally GH should be stimulated by hypoglycemia.

Insulin lowers blood glucose level -> normally stimulating the release of GH. If GH is not increased ->there is a problem.

Functional Pituitary mass: 2. Growth hormone disorders

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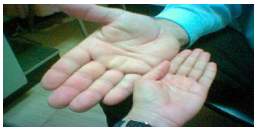
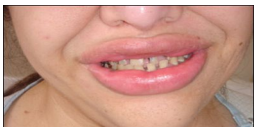
2. Acromegaly





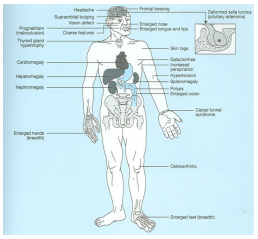


Table 1. Clinical Features of Acromegaly. It is not important to memorize, just read it

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

Evaluation of acromegaly:

C: Clinical

Function : Sweating, Enlargement (acral, face gross features, heart, tongue Jaw, gigantism in children , Galactorrhea)
Mass-effect (mechanical pressure, hypopituitarism)
HTN,CHF, OSA,constipation
O/E: Visual field defect (Bitemporal hemianopia)
Gross features of Acromegaly

B: Biochemical

Pituitary Function (LH,FSH.PRL, TSH, ACTH, cortisol,testosterone, T4)
Screen: IGF-1 insulin like growth factor,not growth hormone
Confirmatory Test: 75 g oral glucose tolerance test (OGTT) for GH suppression
Fasting and random blood sugar, HbA1c
Lipid profile

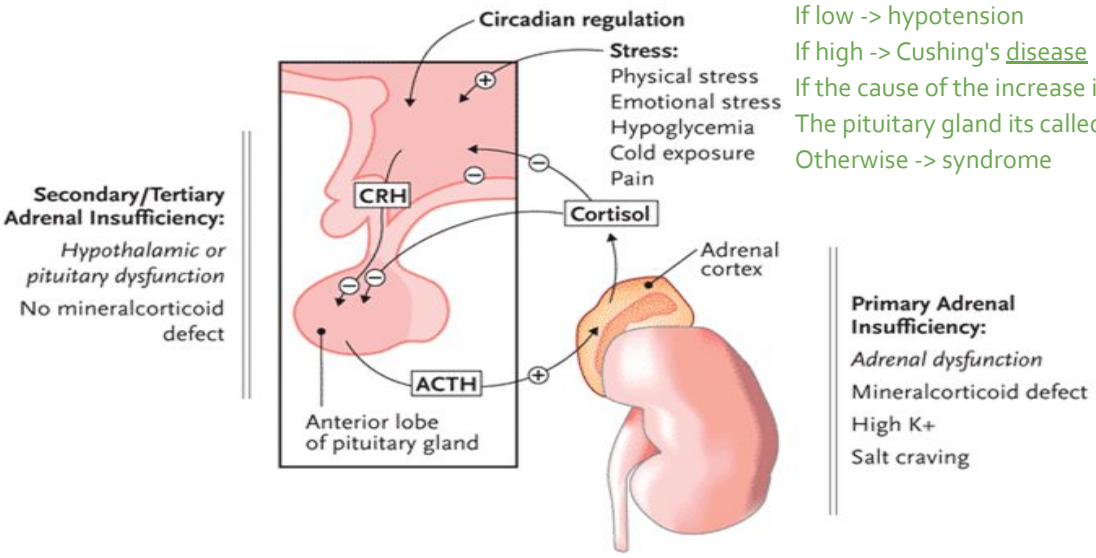
A: Anatomical

MRI +Colonoscopy because acromegaly can cause colon polyps(precursor of colon cancer)
Echo: Cardiac disease is a major cause of morbidity and mortality
50% died before age of 50
HTN in 40%, LVH (Left Ventricular Hypertrophy) in 50%, Diastolic dysfunction as an early sign of cardiomyopathy

Treatment

Surgical, Medical (Somatostatin analogue), Radiation

Functional Pituitary mass: 3. ACTH− Disorders



If low -> hypotension
If high -> Cushing's disease
If the cause of the increase is from The pituitary gland its called Cushing's disease
Otherwise -> syndrome

1. Low cortisol (Hypoadrenalism)

Symptoms:

Nausea, Vomiting, abdominal pain, Diarrhea

Dizziness and weakness, Tiredness, Muscle ache

Hypotension

Weight loss

Management:

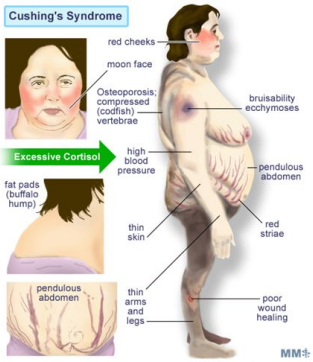
Surgery − Cortisol replacement

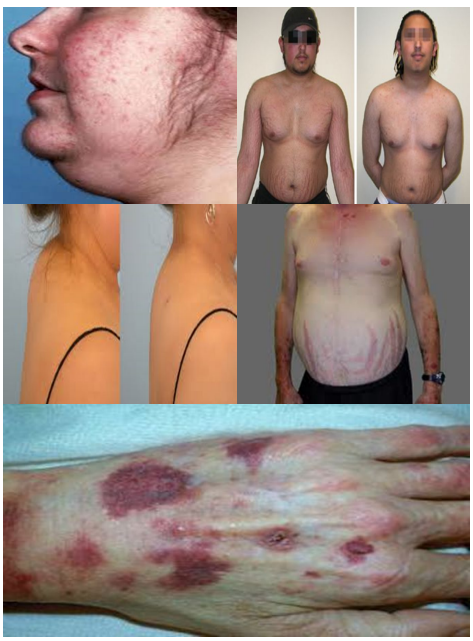
13:43

2. High cortisol (cushing's)

Symptoms:

Fat pad (buffalo hump)
Red cheeks
Moon face
Osteoporosis (codfish/compressed vertebrae)
High blood pressure
Red/purple striae (wide >1cm)
Thin skin
Bruisability
Pendulous abdomen
Poor wound healing
Thin arms and legs
Hirsutism in women
Ecchymosis
Enlarged central body





Functional Pituitary mass: 3. ACTH- Disorders

2. High cortisol (cushing's)

Evaluation of cushing's:

C: Clinical	Function: Hirsutism, acne, easily bruising DM,HTN, irregular period, proximal weakness, recurrent infections, depression O/E: hirsutism, acne, moon face, central obesity, stria, proximal weakness, supraclavicular fat pad,
B: Biochemical	Screening tests: High cortisol, high ACH Confirmatory tests: o 24hrs for UFC o 1MG DST o Midnight salivary cortisol
A: Anatomical	MRI
Treatment	Surgical, Medical (Somatostatin analogue), Radiation

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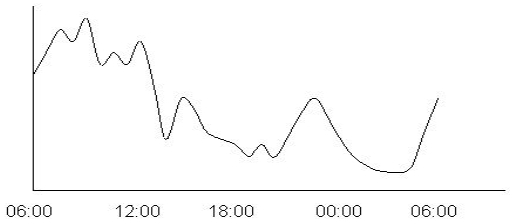
HPA – Axis

Normal:

Circadian rhythm of cortisol secretion Early morning cortisol between 8-9 am.



Highest at morning lowest at night

Excessive cortisol:

80% HTN

LVH left ventricular hypertrophy

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

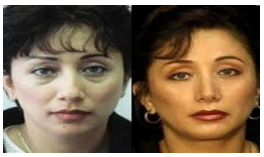
Glucose intolerance in 60%, control of hyperglycemia

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

thin skin⟶ difficult IV cannulation, poor wound healing

Functional Pituitary mass: 4. TSH Disorders

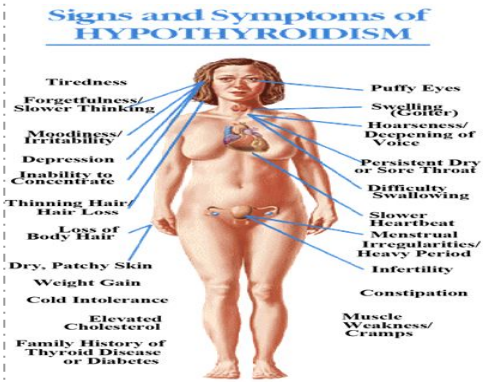
1. Hypothyroidism



Evaluation of central hypothyroidism:

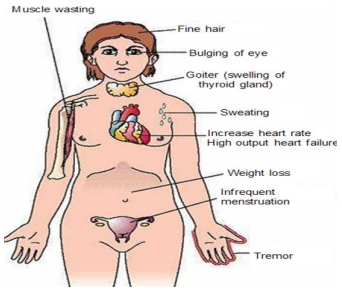
C: Clinical	Function : fatigue, weight gain, irregular menses, dry skin, depression, cold intolerance, increase sleep, slow thinking O/E: obesity, Depressed face, eye brow
B: Biochemical	Low T4 , Low TSH
A: Anatomical	MRI
Treatment	Thyroxine replacement Surgical removal of pituitary adenoma if large

How can we differentiate between central hypothyroidism and primary hypothyroidism?
First, central hypothyroidism is due to disorder in the pituitary gland, while primary hypothyroidism is related to the thyroid gland.
So, if we have Low T4, T3 and Low TSH it indicate Central hypothyroidism. In primary hypothyroidism TSH will be normal



2. Hyperthyroidism

TSH producing adenoma:
Very rare < 2.8 %
Signs of hyperthyroidism
High TSH, FT4, FT3 , in primary hyperthyroidism, TSH Should be normal.
treatment preop with anti-thyroid meds
Surgical resection of adenoma
Medical therapy: Somatostatin Analogue



Functional Pituitary mass: 5. Gonadotroph Adenoma

Gonadotroph Adenoma

Treatment:
Surgical resection if large
Radiation therapy

Gonadotroph adenoma vs. menopause and ovarian failure

- High FSH with low LH. Mostly asymptomatic
- High serum free alpha subunit.
- High estridiol, FSH, thickened endometrium and polycystic ovaries.

Assessment of pituitary function

- History
- Baseline:
  - o TSH, FT4
  - o LH, FSH, and (Testosterone or Estradiol)
  - o Prolactin
  - o GH, IGF-I
  - o ACTH, cortisol and electrolyte
- 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:
  - o maybe need to be covered with stress dose of HC

Summary

	Clinical	Biochemical	Anatomical	Treatment
Non- functional pituitary adenoma	Asymptomtic Mass-effect : mechanical pressure, hypopituitarism, visual (bitemporal hemianopia) Gonadal hypersecretion.	All pituitary hormones: not high But prolactin: low ,high, normal	MRI	Surgery Adjunctive therapy: o Radiation therapy o Dopamine agonist o Somatostatin analogue
Prolactinoma	oligomenorrhea, amenorrhea, infertility, Galactorrhea. Mass-effect (mechanical pressure, hypopituitarism). Sexual dysfunction (in male). Visual field defect (Bitemporal hemianopia). Nipple discharge.	PRL : High TSH: R/O Hypothyroidism(primary) IGF-1: R/O acromegaly co-secretion	MRI	Medical (Dopamine agonist)
GH deficiency	Short stature Mass-effect (mechanical pressure, hypopituitarism)	Screen: IGF-1 clonidine stimulation test glucagon stimulation exercise testing, arginine-GHRH insulin tolerance test	X-ray of hands, MRI	GH replacement
Acromegaly	Sweating, Enlargement (acral, face gross features, heart, tongue Jaw, gigantism in children, Galactorrhea	Glucose tolerance test	MRI Echo	Surgical, Medical (Somatostatin analogue), Radiation
Cushing's syndrome	moon face, Hirsutism, acne, supraclavicular fat pad, recurrent infections, depression, stria.	High cortisol , high ACH 24hrs for UFC 1MG DST Midnight salivary cortisol	MRI	Surgical – Medical – Radiation
Central hypothyroidism	fatigue, weight gain, irregular menses, dry skin, depression, cold intolerance, slow thinking. obesity, Depressed face, eye brow	Low T4 , Low TSH	MRI	Thyroxine replacement Surgical

Quick Revision

Anterior pituitary is developed from: oropharynx, while posterior pituitary from the floor of the 3rd ventricle.
Most common functional adenoma is **prolactin** producing adenoma.
Prolactinoma is the only Disorder that we use medications as first line of treatment.
Usually prolactinomas in women are microprolactinomas, while in men macroprolactinomas
GH is pulsatile, so to diagnose GH deficiency we use Insulin Tolerance Test. And to diagnose acromegaly We use Glucose Tolerance Test.
In the beginning of the day, cortisol is very high then it decreases during the day.
Central hypothyroidism: TSH, T4 and T3 are decreased, while in primary Hypothyroidism: TSH is normal.
TSH producing adenomas are very rare.

MCQs

1. development of pituitary cells is controlled by which set of transcription growth factor?
A. prob-1
B. Pit-1
C. Pitx2
D. All

2. Macroprolactinomas occur in

A. 90% of men
B. 90% of women
C. 60% of men
D. 60% of women

3. Which of the following is diagnostic test of Acromegaly?

A. IGF-1
B. LH and FSH testing
C. Insulin tolerance test
D. Glucose tolerance test

4. In prolactinoma, first line of treatment is?

A. Medical
B. Surgical
C. Radiation
D. None

5. Pituitary gland measures ?

A. 15x10x6 mm
B. 15x5x6 mm
C. 10x7x12 mm
D. 15x10x7 mm

6. Pituitary Adenoma is related to what gene ?

A. MEN1
B. Gs-alpha
C. PTTG gene
D. All

7. We confirm abnormal decrease in hormones by ?

A. Suppressing it
B. Stimulating it
C. All
D. None

8. management of hypoadrenalism ?

A. Cortisol replacement
B. Radiation
C. Surgical
D. None

9. A 40 years old man presented to the clinic with a complaint of a decrease in visual field. Evaluation shows an enlarged pituitary mass. His doctor prescribed oral medications in which his vision improved within a few days. What is most likely the diagnosis?

A. ACTH secreting pituitary macroadenoma

B. FSH/LH secreting pituitary macroadenoma

C. TSH secreting pituitary adenoma

D. Prolactin secreting pituitary macroadenoma

1.D 2.C 3.D 4.A 5.A 6.D 7.B 8.A 9.D