ANTERIOR PITUITARY DISORDERS

Editing file

Lecture 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.

- Important
- Original content
- Only in girls slides
- Only in boys slides
- Doctor's notes

Introduction

Skip

Embryology overview:

Pituitary development

- 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.

Anterior pituitary

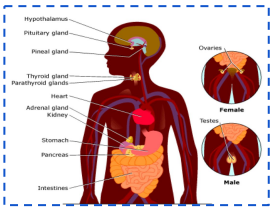
Rathke's pouch

- It's an Ectodermal evagination of oropharynx.
- **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

Posterior pituitary

- Neural cells as an outpouching from the floor of 3rd ventricle.

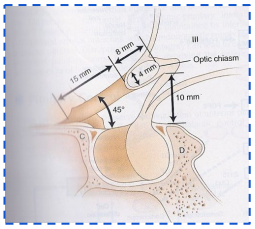
Anatomy overview:



Sella turcica:

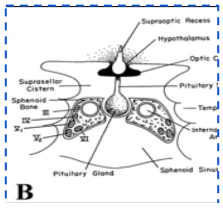
- Pituitary gland is protected by sella turcica which lies at the base of the skull (sphenoid body)..

Relations of pituitary gland:



Roof: Diaphragma sellae(Pituitary stalk and its blood vessels pass through the diaphragm)
Floor: Sphenoid sinus
Lateral walls: Cavernous sinus

- Containing III, IV, VI, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers.
- Both adjacent to temporal lobes



Other info:

Pituitary gland measures: 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.
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

Introduction cont.

Pituitary Function

Anterior pituitary hormones

Synthesis and storage:

Go Look For The Adenoma Please.

- GH LH, FSH, TSH, ACTH and Prolactin.
- A compressive adenoma in pituitary will impair hormone production in this order.

Posterior pituitary hormones

Storage only (not synthesis):

- Oxytocin
- ADH(vasopressin)

NOTE: They're synthesized by hypothalamus.

Summary of all hormones

	Somatotroph	Gonadotroph	Lactotroph	Thyrotroph	Corticotroph
Stimulators	• GHRH • GHS	• GnR • E2	• TR • E2	• TRH	• CRH • AVP • gp-130 • cytokines
Inhibitors	• IGF-1 • Somatostatin • Activins	• Testosterone • E2 • inhibin		• T3, T4 • Dopamine • Somatostatin • GH	• Steroid
Hormone	• GH	• LH,FSH	• PRL	• TSH	• ACTH • POMC
Target Gland	• Liver & other tissues	• Ovary, Testes	• Breast • & other tissues	• Thyroid	• Adrenals
Target Hormone	• IGF-1	• 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

Pituitary disorders

Classified into:

- Anterior pituitary disorders
- Posterior Pituitary disorders
  - e.g. Diabetes insipidus

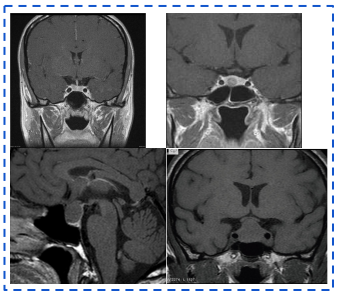
Anterior Pituitary disorders

1 Function:

- **Hypersecretion**: (GH,LH,FSH,PRL,TSH,ACTH)
  - **e.g. Hyperprolactinemia, Acromegaly (↑GH), Cushing's Disease (↑ACTH).**
- **Hyposecretion**: hypopituitarism (isolated, multiple, pan)[1]
  - e.g. **Central hypoadrenalism, hypogonadism, hypothyroidism, GH deficiency or Panhypopituitarism**

2 Types of masses

- **Functioning = Hypersecretion (Oversecretion).**
- **Non- Functioning.**
- Could be with/without mass-effect:
  - Space occupying lesion (compression symptoms[2], hypopituitarism)



Etiology of Pituitary hypothalamic lesion

Not Important

- **Non-Functioning Pituitary Adenomas[3]**
- Pituitary cysts: Rathke's cleft cyst, Mucoceles, Others
- Lymphocytic hypophysitis
- Empty sella syndrome
- Carotid aneurysm and Pituitary abscess
- Metastases in the pituitary (breast, lung, stomach, kidney)
- Malignant pituitary tumors: Functional and non-functional pituitary carcinoma
- **Endocrine active pituitary adenomas**
  - **Prolactinoma[4]** (PRL-oma)
  - **Somatotropinoma** (GH secreting adenoma, Acromegaly)
  - **Corticotropinoma** (ACTH secreting adenoma, Cushing's disease)
  - **Thyrotropinoma** (TSH-oma, rare)
  - Other mixed endocrine active adenomas

1: When a single pituitary hormone is affected, this is called **isolated** pituitary deficiency. When two or more pituitary hormones are affected, this is referred to as multiple pituitary hormone deficiency. **Panhypopituitarism** is a state of reduction of all pituitary hormones.
2: Mass effect in general can cause Nausea, Vomiting & Headache. If the mass is compressing the optic chiasma it will cause bitemporal hemianopia. If it invades the sphenoidal air sinus it will cause CSF leakage throughout the nose
3: Non-functioning adenoma are the most common.
4: Prolactinoma is the most common type of functioning adenomas

Evaluation of pituitary mass

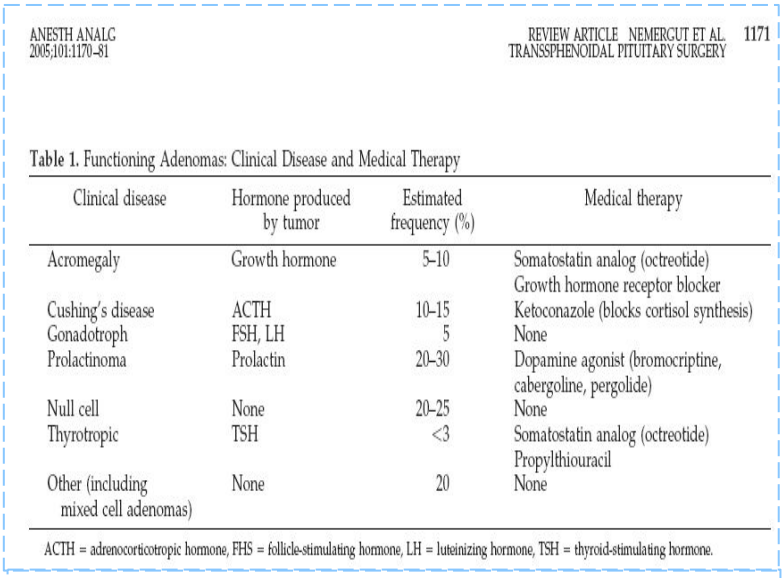
Pituitary adenoma:

- 10 % of all pituitary lesions
- **Genetic-related:**
  - MEN-1
  - Gs-alpha mutation
  - PTTG gene
  - FGF receptor-4

VS
Not Important

Pituitary incidentaloma[1]:

- 1.5 -31% in autopsy (prevalence)
- 10% by MRI most of them <1 cm



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

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.

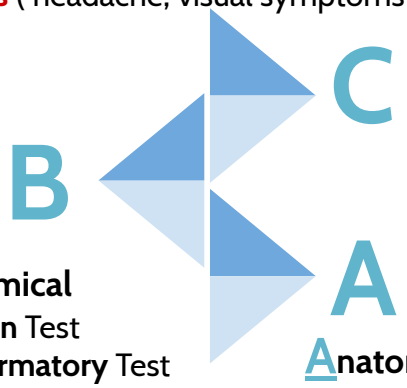
Evaluation of pituitary lesion

To evaluate any patient we start in this order: **CBA**

1) Clinical
2) Biochemical
3) Anatomical.

Clinical[2] (History and Examination)

- **Function** (oversection or hyposecretion)
- **Mass** (headache, visual symptoms)



Biochemical

- **Screen** Test
- **Confirmatory** Test

Anatomical

- **MRI of sella turcica**

- **Then treatment**[3]**:**
  - Surgical – Medical – Radiation
  - Medical – Surgical – Radiation

Non-functional pituitary adenoma

C: Clinical	• **Asymptomatic, incidentaloma** by imaging • Mass-effect (mechanical pressure, **hypopituitarism, visual (bitemporal hemianopia)** • **Gonadal hypersecretion**
B: Biochemical	• **GH,LH,FSH,TSH,ACTH: not high** • PRL : low ,high, normal
A: Anatomical	• MRI
Treatment	• **Surgery if indicated** • **Observation** • **Adjunctive therapy:** - Radiation therapy - Dopamine agonist - Somatostatin analogue

1: In medical or research imaging, an incidental finding (commonly known as an "incidentaloma") is an unanticipated finding which is not related to the original diagnostic inquiry.

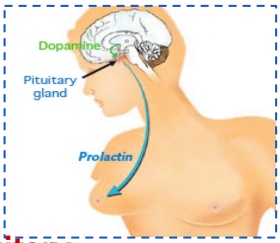
2: To assess the patient you should approach in 2 ways. **First approach:** ask about **mass effect** symptoms caused by the tumor (visual field defect, CSF rhinorrhea, headache, projectile vomiting) **Second approach:** assess the gland function by asking the patient about specific hormonal changes. E.g GH (excessive sweating, clothes size changes)

3: All adenomas are surgically removed **EXCEPT** prolactinoma, medically treated (Bromocriptine or Cabergoline)

Functional pituitary mass (Prolactinoma)

A- Prolactinoma

(High Prolactin + Mass)



- **Some growth hormone (GH)–producing tumors also co-secrete PRL.**

- **Most common of functional pituitary adenoma**, 25-30% of all pituitary adenoma.
- Prolactinomas in **women:**[1]
  - 90% present with **micro**prolactinomas
- Prolactinomas in **men:**[1]
  - 60% present with **macro**prolactinomas

What if prolactin was 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.

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[2]: to rule out Primary Hypothyroidism** **IGF-1[2]: to rule out acromegaly with co-secretion of prolactin** (in 15% of cases)
A: Anatomical	MRI
Treatment	• **Medical – Medical – Medical (Dopamine agonist e.g.** Bromocriptine or Cabergoline)[3] • **Surgical- Radiation** (Second line)

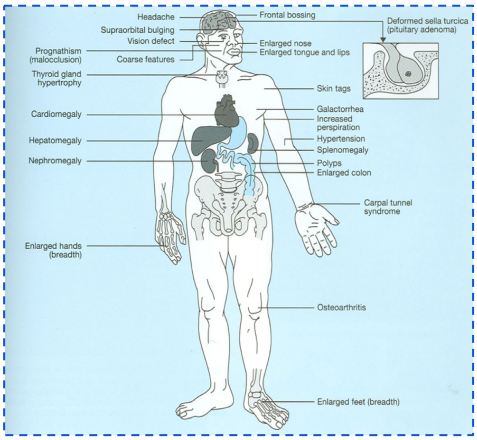
1: The cause of difference between males and females in the size of the tumor (Macro & Micro) is that females usually present early, once they notice any changes in their menstrual cycle. While males tend to ignore the symptoms since they are not specific (fatigue, headache), they seek medical advice later.
2: Before you diagnose the patient with prolactinoma you should rule out Primary hypothyroidism and acromegaly by measuring TSH & IGF-1 respectively.
In case of primary hypothyroidism there will be low T3&T4 and high TSH(due to high TRH). Note that TRH can cause prolactin secretion as well not only TSH.
3: in prolactinomas always start with medical treatment (NOT SURGICAL) even if there is mass effect (Eg. visual field defect)

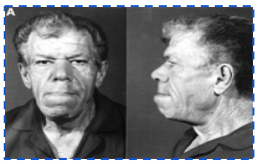
Functional pituitary mass cont. (Acromegaly)

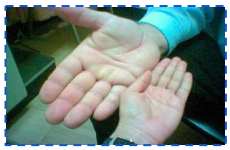
Definition: Acromegaly is a hormonal disorder that results from too much growth hormone (GH) in the body.

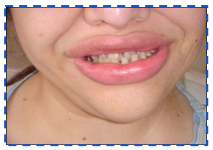
Table 1. Clinical Features of Acromegaly.

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









C: Clinical[1]	• 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** (will be high) • **Confirmatory Test : 75 g OGTT(**Oral glucose tolerance test**)**[2] **tolerance test for GH suppression** • Fasting and random blood sugar, HbA1c • Lipid profile

A: Anatomical	• MRI
	• Echo:
	  ○ **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

Treatment	**Surgical – Medical (Somatostatin analogue)- Radiation**

- Growth usually stops after 3 year from puberty

1: They have high risk for IHD because the have large heart.

2: Doctors can't simply test for the level of growth hormone (GH) in your body because the level varies so much in one day—even in someone without acromegaly. In someone without acromegaly, a higher blood glucose level usually causes the body to stop producing GH (suppress it). Therefore, a doctor will purposely raise your blood glucose level using an OGTT and watch how your GH level responds. **If your GH level doesn't drop to below 1 ng/mL during the OGTT, you have acromegaly.**

GH deficiency

Definition: rare disorder characterized by the inadequate secretion of growth hormone(GH) from the anterior pituitary gland.

Characteristics

- Isolated, panhypopituitarism
- Pituitary tumor **as mass effect** → Growth hormone deficiency
- Diagnosis in children and adult
- Disease in:
  - **Children: Short stature**
  - **Adult:** metabolic syndrome, weight gain and social isolation.

C: Clinical	• **Function : Short stature** • **Mass-effect (mechanical pressure, hypopituitarism)**

B: Biochemical[1]	• Pituitary Function (LH,FSH.PRL, TSH, ACTH, cortisol, testesterone, T4)
	• **Screen: IGF-1**
	• **Dynamic testing:**
	  ○ clonidine stimulation test
	  ○ glucagon stimulation
	  ○ exercise testing,arginine-GHRH
	  ○ **insulin tolerance testing**

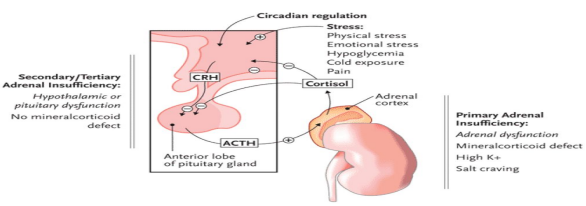
A: Anatomical	• **X-ray of hands: delayed bone age** • MRI
Treatment	• **GH replacement**

ACTH disorders Introduction

ACTH disorders

High Cortisol

- ACTH adenoma → Cushing's disease



Low cortisol

- Hypoadrenalism

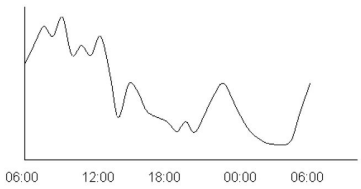
1: If you want to measure the growth hormone in a Short statured patient, you should stimulate GH secretion by making him make him hypoglycemic(by giving him insulin) then measure the GH. If GH is stimulated that means he is normal. If not that confirms the diagnosis of GH deficiency .

Functional pituitary mass cont.

(ACTH disorders)

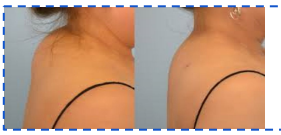
HPA-axis:

- Circadian rhythm of cortisol secretion.
- **Early morning** cortisol between 8-9am (Highest).
- lowest at **midnight.**

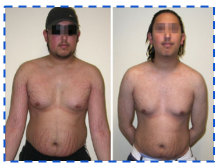


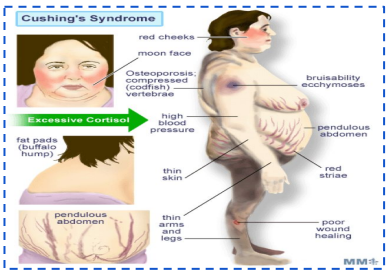
Excessive cortisol:

(ACTH adenoma → Cushing disease)



buffalo hump

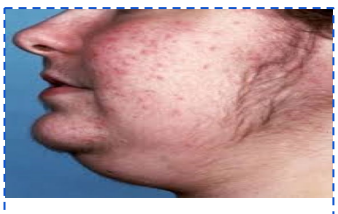




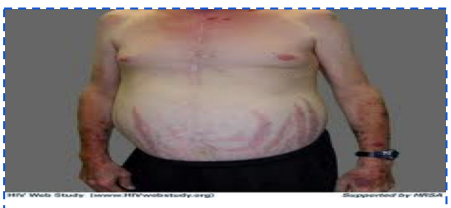
Complications: Not Important

- 80 % HTN
- Left ventricular hypertrophy
- Diastolic dysfunction, interventricular septal hypertrophy
- ECG needed: high QRS voltage, inverted T-wave
- Echocardiogram pre-op
- 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

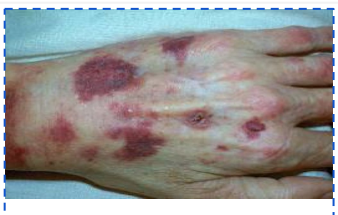
C: Clinical	• Function : **Hirsutism**, acne, easily bur, DM,HTN, irregular period, proximal weakness, recurrent infections, depression • O/E: hirsutism, acne, **moon face,** central obesity, **stria**, proximal weakness, **supraclavicular fat pad** (buffalo hump),
B: Biochemical	Screening test: • **High cortisol , high ACTH** Confirmatory tests: • **24hrs for urine free cortisol (UFC)**[1] • 1MG DST • **Midnight salivary cortisol**[1]
A: Anatomical	• MRI
Treatment	• Surgical – Medical - Radiation



Hirsutism in women



Stria(purple, wide >1cm)



ecchymosis

1: If high this indicates Cushing disease.

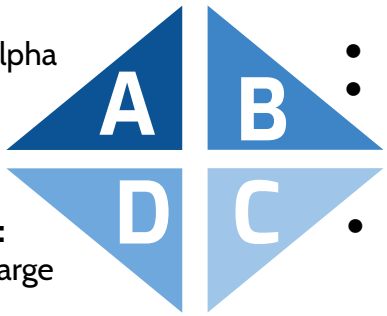
Difference between cushing disease and syndrome: Cushing disease is caused by a **pituitary gland tumor** (usually benign) that over-secretes the hormone ACTH, thus over stimulating the adrenal glands' cortisol production. **Cushing syndrome** refers to the signs and symptoms associated with excess cortisol in the body, **regardless of the cause**, could be due to corticosteroid medications.

Low cortisol (Hypoadrenalism)

Clinical features	1- **Nausea, Vomiting, abdominal pain,** Diarrhea. 2- Dizziness and weakness, Tiredness, Muscle ache. 3- **Hypotension** and Weight loss. 4- **Very dark skin**[1]
Management	• Cortisol replacement

Gonadotroph adenoma Not Important

Gonadotroph adenoma VS menopause & ovarian failure



- High serum alpha subunit
- High FSH
- Low LH
- **Gonadotroph adenoma:**
  - Surgical resection if large
  - Radiation therapy
- **High:**
  - Estradiol
  - FSH
- Thickened endometrium and polycystic ovaries

Assessment of pituitary function

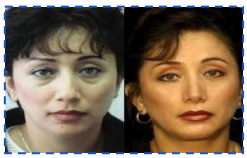
1. Baseline: TSH, FT4, FT3, LH, FSH, Prolactin, GH, IGFI,Testosterone, Estradiol
2. MRI brain
3. Neuropthalmic evaluation of visual field
4. Cardiac and respiratory assessment
5. Anesthesiologist for airway and perioperative monitoring
6. Neurosurgeon
7. ENT for Endonasal evaluation for surgical approach
8. Preop hormonal replacement: all pituitary adenoma should be covered with stress dose of HC

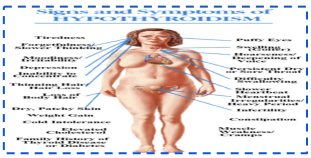
1: Hyperpigmentation occurs because MSH(Melanocyte stimulating hormone) and ACTH share the same precursor molecule(POMC). POMC is cleaved into ACTH, gamma-MSH and beta-lipotropin. The subunit ACTH undergoes further cleavage to produce alpha-MSH, the most important MSH for skin pigmentation.

Central[1] Hypothyroidism

Definition: **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.

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

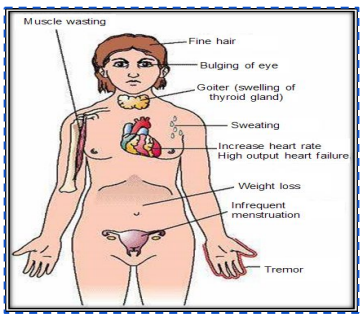




TSH-Producing adenoma (Hyperthyroidism)

Definition: 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 an overactive thyroid (hyperthyroidism).

1. Very rare < 2.8%
2. Signs of hyperthyroidism
3. **High TSH, FT4, FT3**
4. **Treatment preoperative with** anti-thyroid meds
5. Surgical resection of adenoma
6. **Medical therapy:** Somatostatin Analogue



1- **What's the difference between central hypothyroidism and primary hypothyroidism? Central hypothyroidism** is due to disease in the **pituitary** gland while **Primary hypothyroidism** is due to disease in the **thyroid** gland. so we can conclude that both will have low T3,T4 but only central hypothyroidism will have low TSH.

QUIZ!

1) A 35-year-old woman complains of nipple discharge and irregular menses of 5 months duration. Physical examination reveals a milky discharge from both nipples. MRI shows an enlargement of the anterior pituitary. Which of the following is the most likely histologic diagnosis of this patient's pituitary tumor?

(A) Adenoma
(B) Choristoma
(C) Hamartoma
(D) Papilloma

2) A 50-year-old woman presents with a 2-year history of upper truncal obesity and depression. Serum levels of glucose and cortisol are elevated. A CT scan of the abdomen reveals a 2-cm suprarenal mass. The surgical specimen is shown in the image. If this neoplasm is benign, which of the following is the most appropriate diagnosis?

(A) Prolactinoma
(B) Hypothyroidism
(C) Adrenal Adenoma
(D) Hyperthyroidism

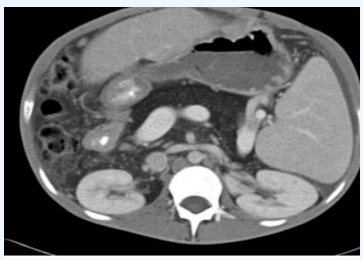
3) A 40-year-old woman notices that her gloves from the previous winter no longer fit her hands. Her friends remark that her facial features have changed in the past year, and that her voice seems deeper. On physical examination, she is afebrile. Her blood pressure is 140/90 mm Hg. She has coarse facial features. There is decreased sensation to pinprick over the palms in the distribution of her thumb and first two fingers. A radiograph of the foot shows an increased amount of soft tissue beneath the calcaneus. A chest radiograph shows cardiomegaly. Laboratory studies indicate a fasting serum glucose level of 138 mg/dL and hemoglobin A 1c level of 8.6%. Which of the following additional test results is most likely to indicate the cause of these physical and laboratory findings?

(A) Elevated serum prolactin level
(B) Failure of growth hormone suppression
(C) Increased serum cortisol level
(D) Increased serum TSH level

4) A previously healthy 30-year-old woman visits her physician complaining of a racing heart, sweating, weight loss, and tremulousness. She appears anxious, and on further questioning reports that her anxiety and restlessness have begun to cause problems at her workplace. Physical examination reveals
tachycardia, moist skin, fine body hair, and bilateral bulging of her eyes.

(A) Gonadotroph adenoma
(B) Hypothyroidism
(C) ACTH Adenoma
(D) Hyperthyroidism

5) A 62-year-old man with a long history of alcoholism presents to the emergency department with steatorrhea and abdominal pain. CT of the abdomen is shown in the image. The intern on duty recalls learning about a drug indicated for acromegaly that may also reduce the secretion of pancreatic fluids and possibly decrease the patient's pain. The drug works by mimicking the levels of which hormone?



(A) Secretin
(B) Gastrin
(C) Cholecystokinin
(D) Somatostatin

Answers

1. A, 2. C, 3. B, 4. D, 5. D

Team Leaders

Abdulrahman Bedaiwi & Jude Alotaibi

Team Members

- Alhanouf Alhaluli
- Ajeed Alrashoud
- Jehad Alorainy
- Mashal Abaalkhail
- Mohannad Alqarni
- Rahaf Alshabri
- Rakan Alfaifi
- Rawan Alzayed
- Rema Almutawa

Thank you!

Give us your feedback!