The Ups & Downs of the NeuroEndocrine System

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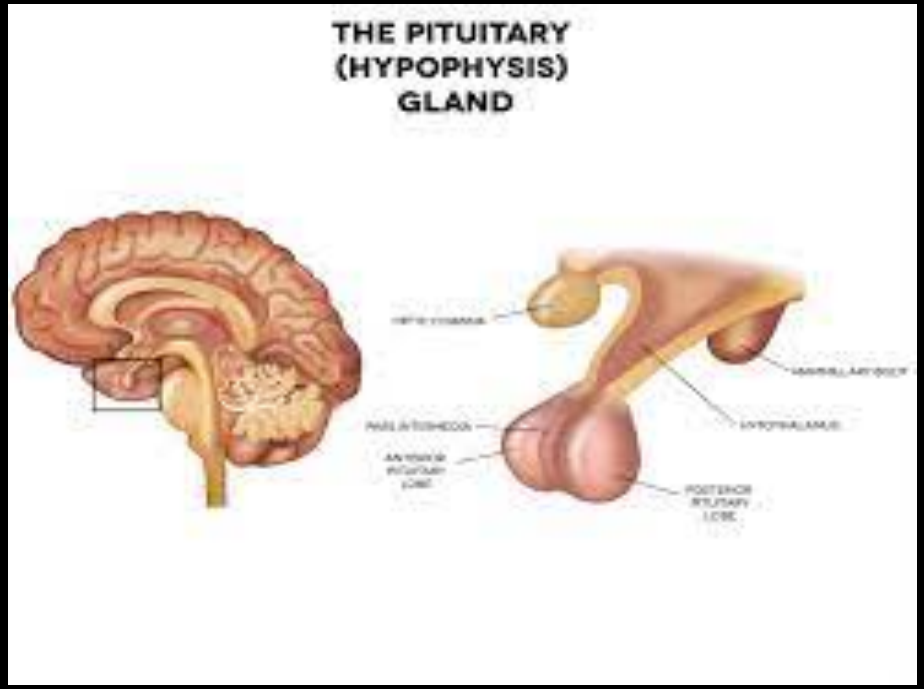
I have nothing to disclose

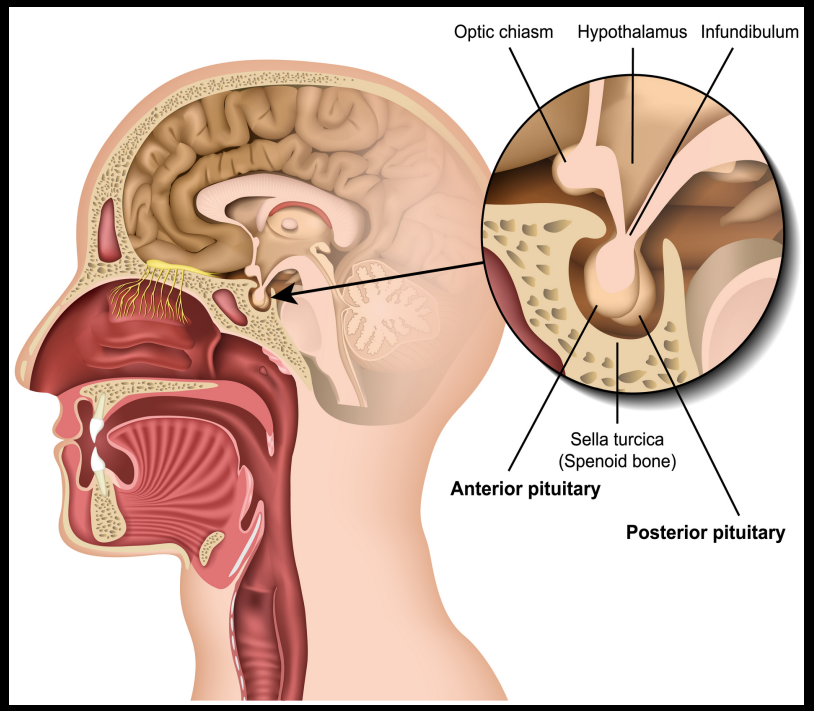
Objectives

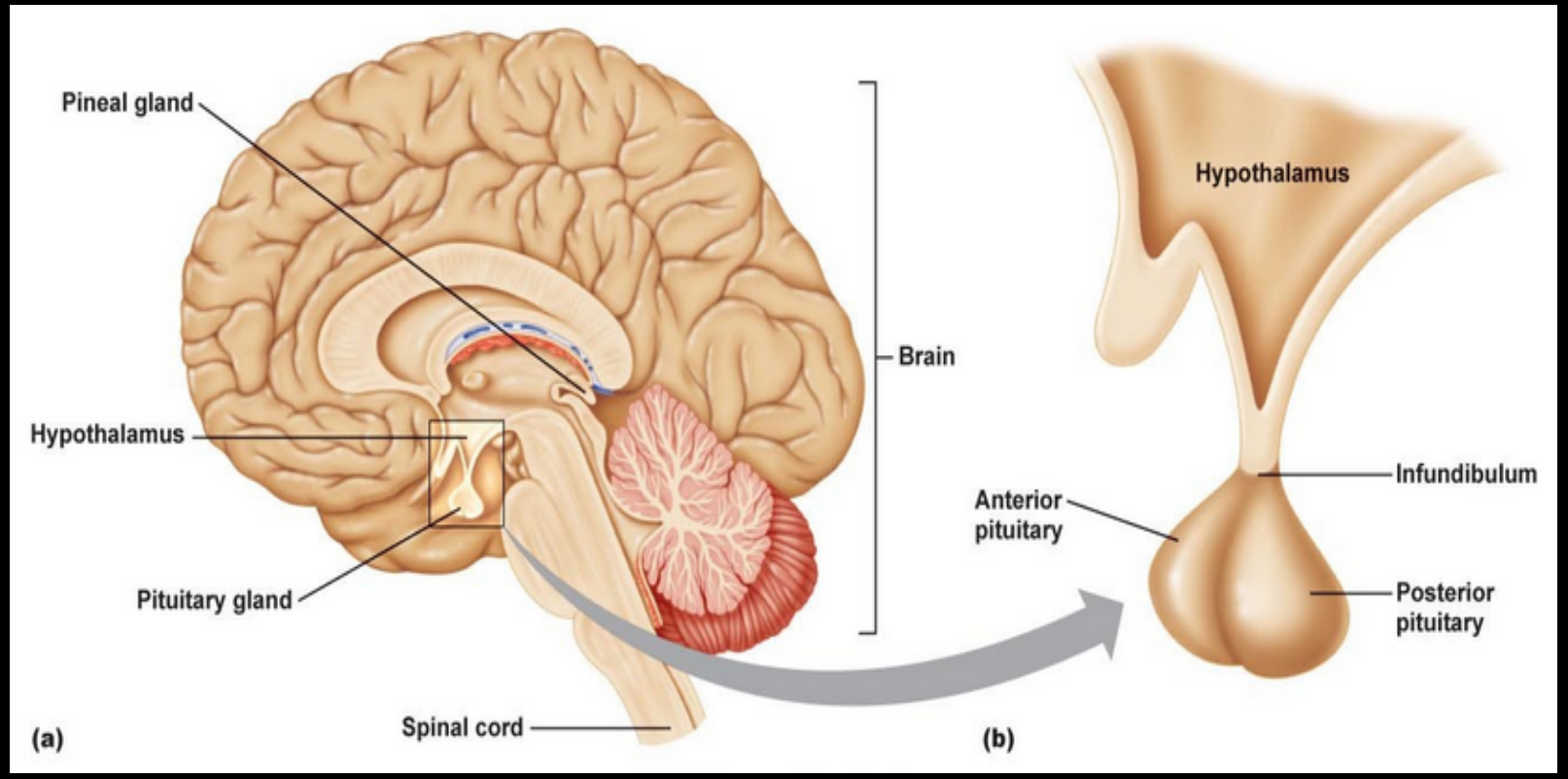
- Identify the hormones secreted by the Pituitary Gland and their action
- Describe the pathophysiology, management/treatment for patients with GH deficiency/excess,, adrenal insufficiency and Cushing Syndrome, SIADH, CSW, CDI

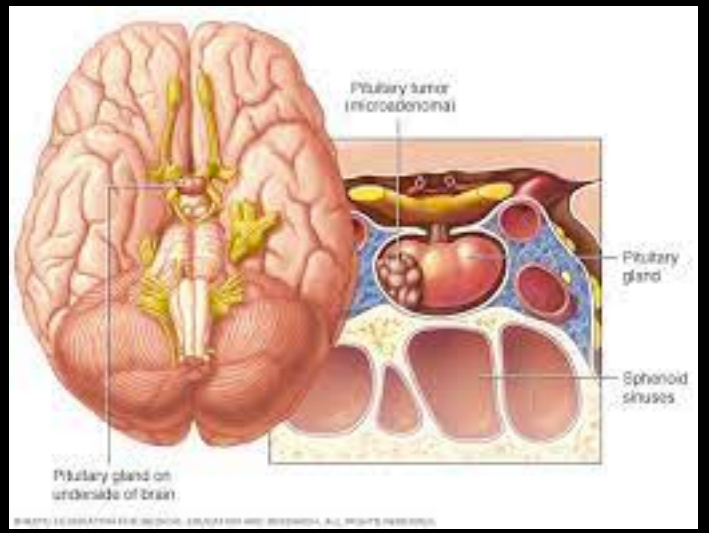


Anatomy & Physiology of the Pituitary Gland

- Pea-size gland located in a protective boney enclosure called the ***Sella Turcica,*** located at the base of the skull.
- Connected to the hypothalamus by the infundibulum; aka pituitary stalk, allowing communication between the pituitary gland and hypothalmus
- Comprised of two lobes
  a. Anterior lobe (adenohypophysis)
  b. Posterior lobe (neurohypophysis)





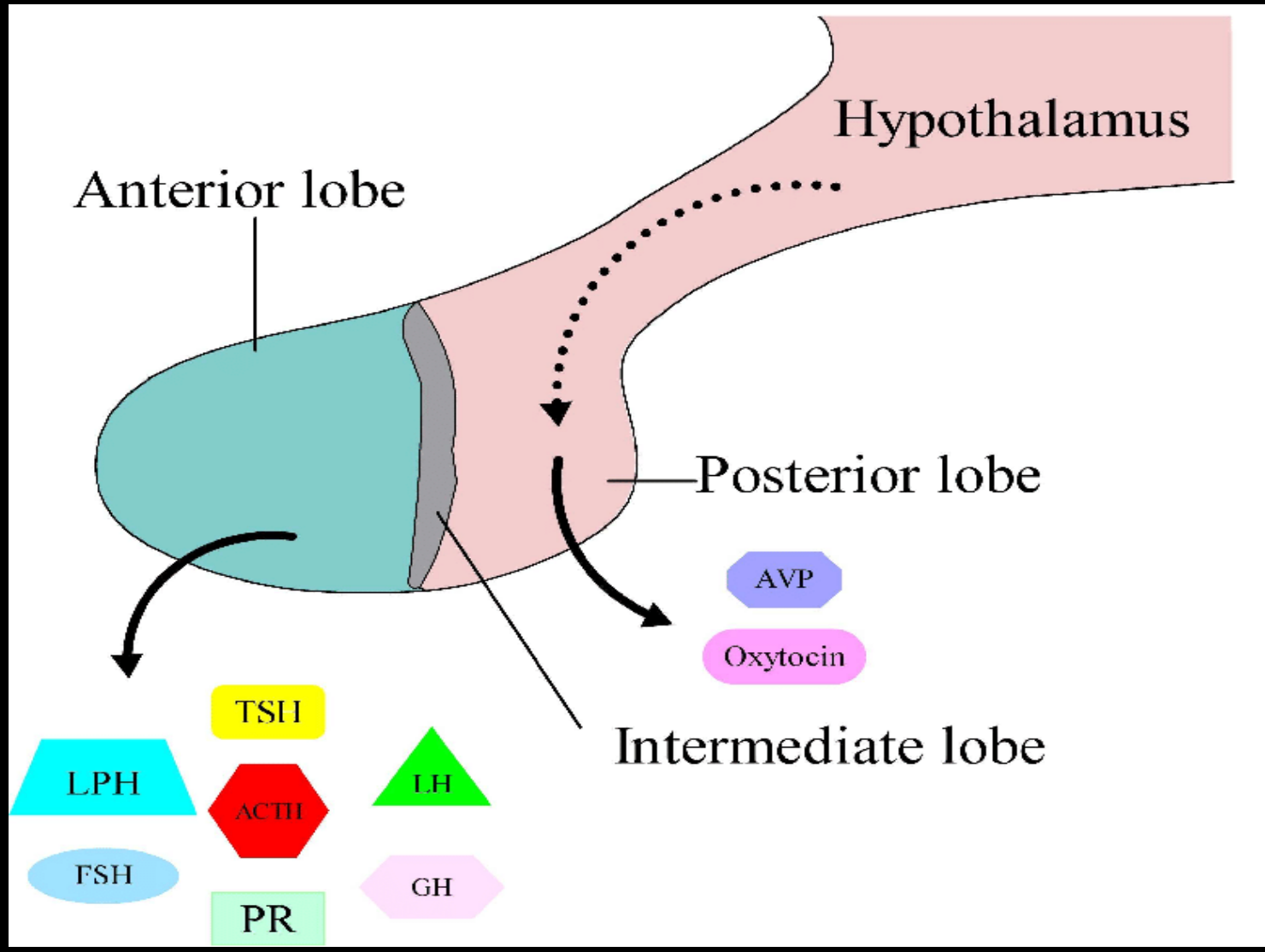


Pituitary Gland-Anterior Lobe

Type of cell	Hormone Secreted
Somatotropes	Human growth hormone (hGH): stimulates growth of bone, cartilage, and muscle.
Corticotropes	Adrenocorticotropin (ACTH): stimulates glucocorticoid & mineralocorticoids. Responsible for androgen production by the adrenal cortex.
Thyrotropes	Thyroid stimulating hormone (TSH): stimulates the synthesis and secretion of thyroid hormones.
Gonadotropes	Gonadotropic hormones- Lutenizing hormone (LH) & Follicle stimulating hormone (SH): stimulates growth and maturity. Is responsible for normal functioning of primary & secondary sex organs.
Lactotropes	Prolactin (PRL): stimulates the growth of mammary tissue and promotes lactation.

Pituitary Gland-Posterior Lob

- The posterior lobe differs from the anterior lobe in that it directly extends from the hypothalamus.
- The posterior lobe contains magnocellular neurosecretory cells that are synthesized by the hypothalamus & are stored and secreted by the posterior lobe



Pituitary Gland-Posterior Lobe

Antidiuretic Hormone

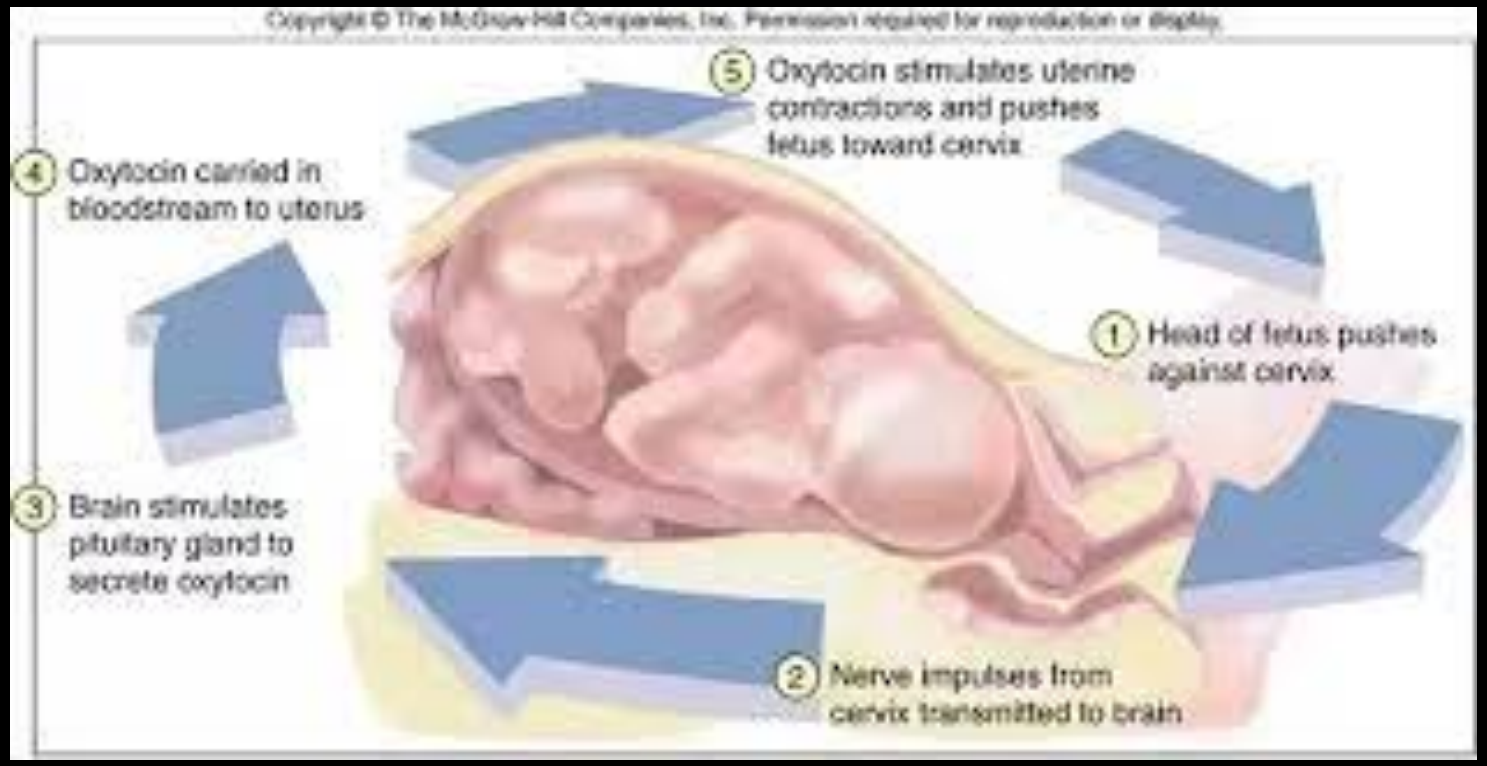
- AKA vasopressin & arginine vasopressin (A/G)
- Majority of ADH secreted in the hypothalamus & responsible for reabsorption of water by the kidney

Oxytocin

- One of the few hormones that provides a “feedback loop” e.g: Uterine contractions stimulate the release of oxytocin in the posterior lobe of the pituitary → stimulation of uterine contractions.

- Responsible for ejection of milk from mammary alveoli into ducts

Posterior Lobe–Feedback loop



Growth Hormone Deficiency in Children- Pituitary Dwarfism

Growth Hormone Deficiency in Adults

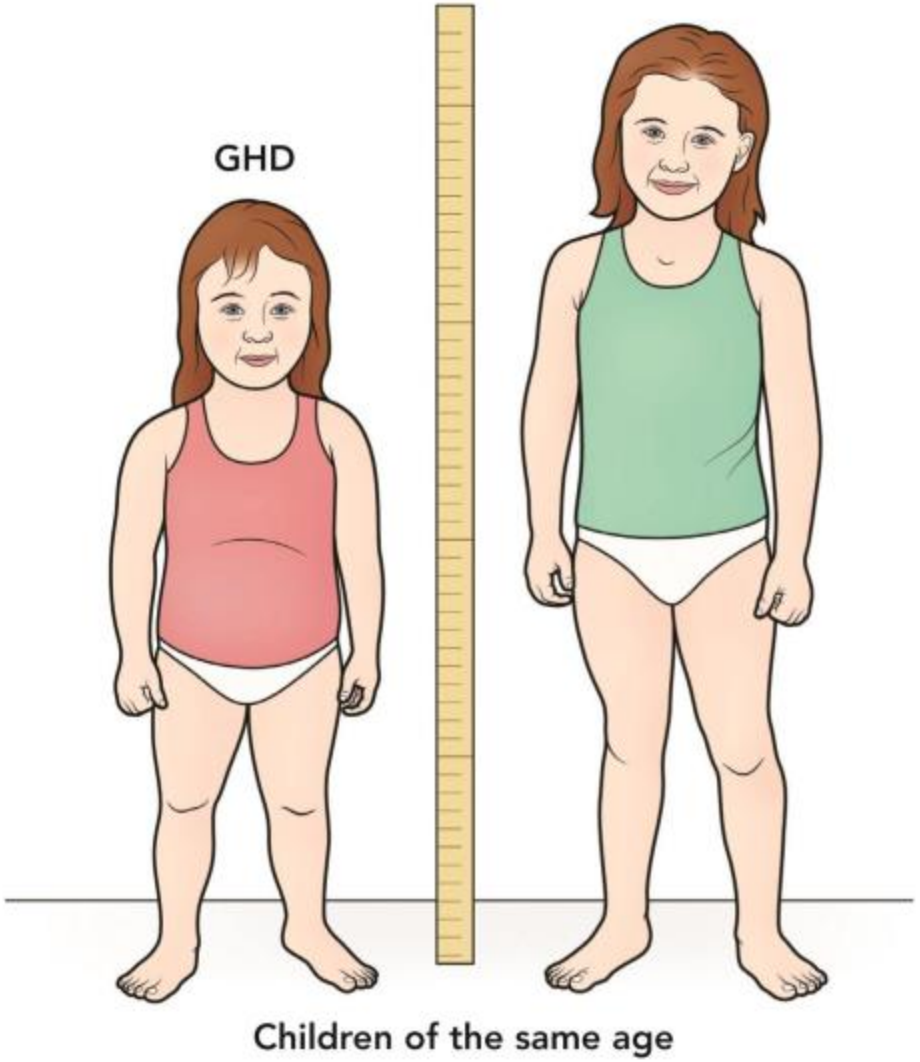
GH Deficiency: Epidemiology & Etiology

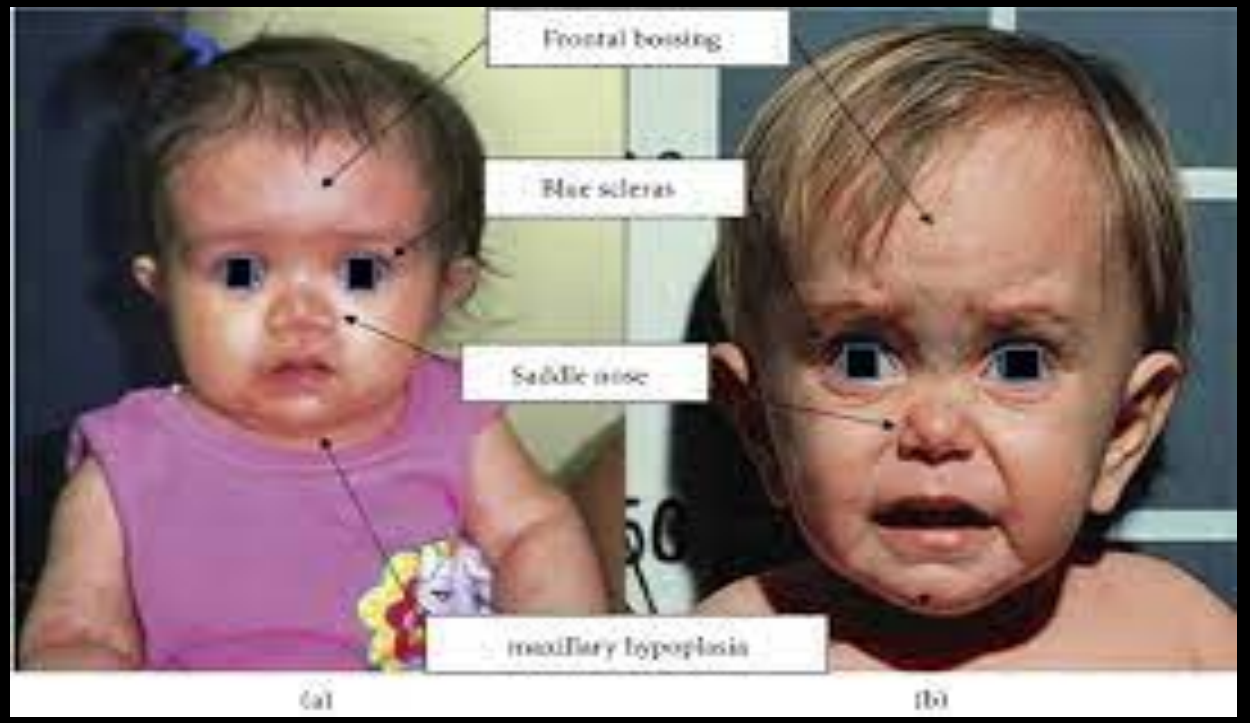
- GH deficiency is the result of underproduction of the Growth Hormone causing the child to have features that include short stature with normal body proportions & characterized by growth velocity & delayed skeletal maturity.
  - ❖ Considered to be a rare disorder that requires early recognition, diagnosis & treatment in order to improve outcomes.
- Epidemiology
  - ❖ Prevalence: 1 in 4000/10,000 live births/year.
- Etiology
  - ❖ Genetic: Due to mutations of the GH gene. Multiple gene mutations identified to date.
  - ❖ Acquired: Multiple mechanisms including direct affect on hypothalamus; tumors of pituitary gland and other CNS tumors including germinoma, craniopharyngioma, optic glioma, etc.; head trauma, CNS infections, surgery, vascular events.

Data Assessment

- Subjective
  - Headache.
  - Parents may note a decreased growth pattern.
  - Parent or child may note excessive thirst and urination.

- Objective
  - Evidence on growth chart of slow or absent growth or short stature.
  - Normal growth & development for first 6 months of life; child noted to have growth deficit.
  - Evidence of child falling below the 5 percentile on the growth chart.
  - Absent or delayed development of secondary sex development in adolescents.
  - Cephalofacial features: appearance of “baby face”
  - Upper-to-lower body ration may be greater than normal. Appearance similar to infantile proportions.





Diagnostic Work-up

- Multistep process that includes physical examination, biochemical testing & radiological imaging.
- Complete history and physical examination.
  - ❖ Including height, weight, body proportions.
- Radiological imaging
  - ❖ Plain x-ray of extremities to determine bone age.
  - ❖ Dual-energy x-ray (DEXA scan) to aide in determining bone age.
  - ❖ CT and MRI imaging of the brain to rule out evidence of structural causes for GH deficiency.
  - ❖ Skull x-ray to assess condition of sella turcica; i.e. erosion of sella turcica may indicate pituitary tumor.
- Laboratory testing
  - ❖ May include thyroid function tests to rule out thyroid disease as cause of symptoms.
  - ❖ CMP, CBC, Celiac screen, inflammatory markers to rule out other causes of symptoms.
  - ❖ GH stimulation: using glucagon test & arginine stimulation test.
  - ❖ Measurement of IGF-1 (Insulin growth factor 1) and IGFP-3 (Insulin Grow Factor binding protein)
  - ❖ Genetic Investigation: Several identified mutations.

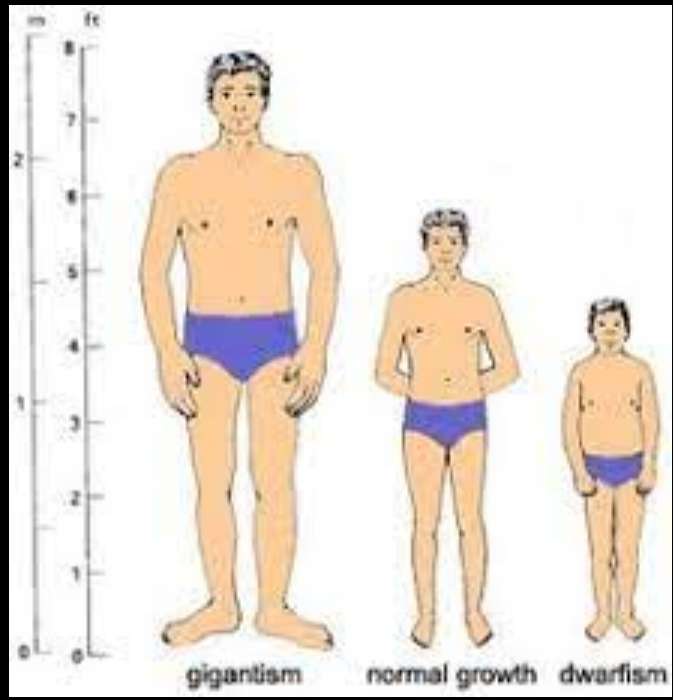
Management

- Physical Assessment
  - ❖ Measure and document height/weight at each patient encounter & compare with standardized growth chart.
  - ❖ Assess for age-appropriate development of secondary sex characteristics
- Interventions
  - ❖ Recombinant GH replacement therapy: initial GH dose of 0.16-0.24 mg/kg/week (22–35 mcg/kg/day with individualization of subsequent dosing.
  - ❖ Administered IM or SQ
- Education/Anticipatory Guidance
  - ❖ Provide parents & children with patient education materials reviewing medication action, adverse effects & importance of medication adherence.
  - ❖ Provide instruction to parents/caregiver on proper technique of administering medication
  - ❖ Review with parents or caregiver signs & symptoms to be reported immediately

Overview: GH-Deficiency Adult

- Occurs as a direct result of insufficient production of growth hormone in anterior pituitary lobe.

- Epidemiology
  - ❖ 6,000/year of newly diagnosed GH deficiency in adults.
  - ❖ 15-20% of cases attributed to childhood GHD.
  - ❖ Estimated prevalence is 1/10,000 in the population.
  - ❖ Individuals receiving cranial radiation prevalence 45%.



Etiology

- Congenital Causes

  - ❖ 15-20% of adults with GH deficiency are continuation from childhood.
  - ❖ Genetic mutations; as with children several genes involved.

- Acquired Causes

  - ❖ Development of tumors in hypothalamus or pituitary gland including pituitary adenoma, Rathke cleft cyst, craniopharyngioma, glioma, germinoma & metastatic tumors including breast, lung, colon & prostate)
  - ❖ Direct result of cranial radiation.
  - ❖ Neurosurgical interventions involving the pituitary gland & hypothalamus.
  - ❖ Cranial trauma including head injury, vascular event including stroke & SAH, infections of the CNS.
  - ❖ Other acquired causes including infiltrative and granulomatous disease; eg sarcoidosis, TB.

Data Assessment

- Subjective
  - Patients may complain of low energy, malaise & depressed mood. .
  - Weight gain, exercise intolerance, muscle weakness.
  - Decreased concentration & memory.
  - Difficulty sleeping.
  - Dry skin
- Objective
  - Impaired glucose tolerance.
  - Elevated triglyceride, low high-density lipoprotein levels.
  - History of head injury, RT, stroke etc.
  - Short stature.
  - Increased body fat (abdominal & central trunk region).
  - Decreased lean body mass.
  - Decreased bone density
  - Hypertension may be present.
  - Thin dry skin.

Diagnostic Work-Up

- Reserved for the individuals with high probability of disease
  - ❖ Patients with h/o trauma, cranial RT, signs of pituitary dysfunction
- Diagnosed by provocative testing.
  - ❖ Insulin tolerance test (contraindicated in elderly patients & individuals with known seizure & cardiac history.
  - ❖ Serum insulin-like growth factor (IGF-1).
  - ❖ Radiologic imaging including MRI brain.
- Other lab work
  - ❖ Lipid profile: not diagnostic; adults with GH deficiency frequently found to have dyslipidemia

Management

- Medical
  - Growth Hormone (GH) replacement with recombinant human GH.
  - Dosing recommendations individualized vs. weight-based.
  - Dosing based on sex, estrogen status & age.
  - Adults with Diabetes Mellitus may require medication dose adjustment of diabetes medication.
  - Initial dosing 0.1-0.2 mg SQ daily in evening.
  - Replacement therapy titrated according individual response, side effects, IGF-1 levels.
  - Women typically will require higher doses; especially in those women taking estrogen therapy.
  - Adults with Diabetes Mellitus may require slower titration.

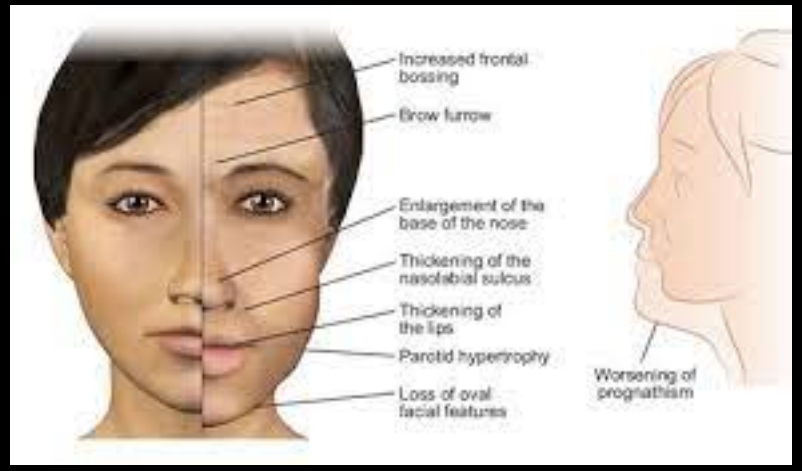
- Patient Education
  - Provide patient or care giver with patient education materials reviewing medication action, adverse effects & importance of medication adherence.
  - Provide patient or care giver instruction on proper technique of administering medication.

Patient Outcomes

- Children
  - ❖ Adherence to hormone replacement therapy.
  - ❖ Acceleration of growth velocity to promote normalization of growth in first year of treatment.
  - ❖ Expected rates of growth 4-6 inches (10-15cm).
  - ❖ Attainment of normal adult height appropriate for genetic potential; ie parent height.
  - ❖ Increased bone mineral density and lean body mass; decreased fat mass

- Adults
  - ❖ Adherence to treatment plan.
  - ❖ Improvement in body fat distribution & lean muscle mass.
  - ❖ Improved bone density.
  - ❖ Improved cardiac function
  - ❖ Patient will subjectively note improved exercise tolerance, decreased fatigue, improved memory, concentration & improved quality of life.

Growth Hormone Excess:
Gigantism
Acromegaly



Overview-Gigantism

- Rare disorder in the United States; occurrence approximately 2,367 children/adolescents, prevalence 0.6%
- Affects primarily prepubertal children; equal distribution between boys & girls affected by this disorder
- Associated with pituitary adenomas; individuals may also present with hyperprolactinemia
- Other causes include familial or sporadic genetic defects resulting in hypersecretion of growth hormone
- May also be associated with conditions including neurofibromatosis or tuberous sclerosis

Overview-Acromegly

- Excessive GH secretion occurs after puberty & when epiphyseal plate fusion has taken place
- Hallmark features include ***gradual*** enlargement of feet, hands & facial features
- Incidence 3-4 per/million each year. Prevalence 60/1,000,000
- Mean age at presentation 44 years of age
- No differences in race, ethnicity, sex
- May be associated with other conditions including hyperprolactinemia, multiple endocrine neoplasia including pituitary adenoma & high risk for developing malignancies including thyroid cancer

Data Assessment

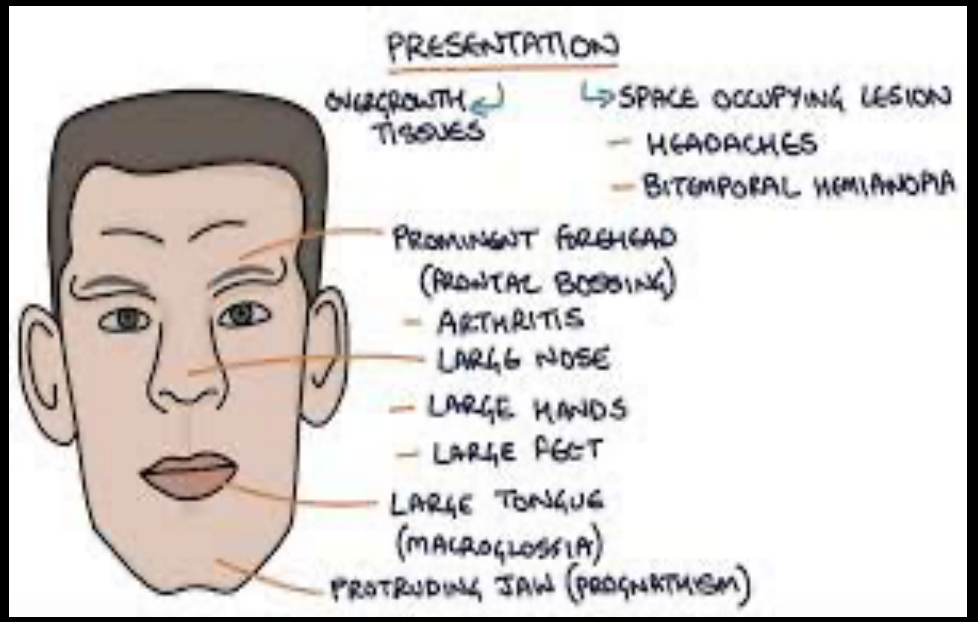
- Subjective

  - ❖ Patients may note changes in vision/visual deficit.
  - ❖ Notice over time weight gain increased hand size, need for increased shoe size or ring size. Notice change in facial features, skin texture
  - ❖ Develop increasing heat intolerance, excessive sweating.
  - ❖ Complain of lethargy, generalized weakness, arthalgias and shortness of breath.
  - ❖ Complain of headache.
  - ❖ Changes in menstrual cycle, decreased libido, erectile dysfunction, galactorrhea.
  - ❖ Snoring, sleep apnea, narcolepsy.

Data Assessment

- Objective

  - Hypertensive
  - Course facial features, tall stature, mild to moderate obesity & macroencephaly.
  - Cardiac features including presence of murmur, arrhythmia.
  - Neurological deficits including papilledema, VF deficits, diplopia & other CN III, IV & VI deficits.

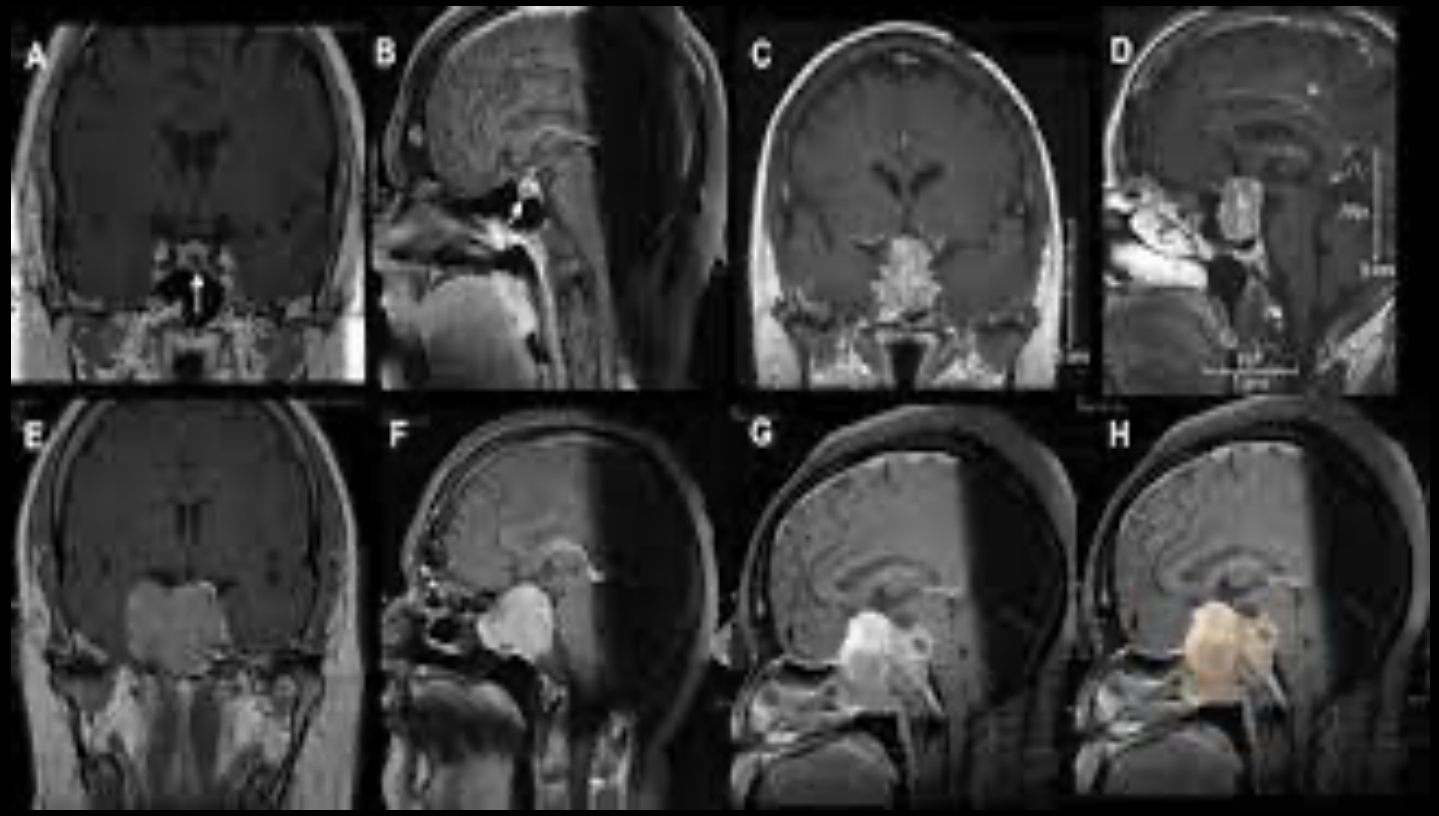


Diagnostic Work-Up

- Radiographic work-up/r/o mass
  - ❖ Skull x-ray
  - ❖ CT scan head with/without contrast
  - ❖ MRI brain with/without gadolinium

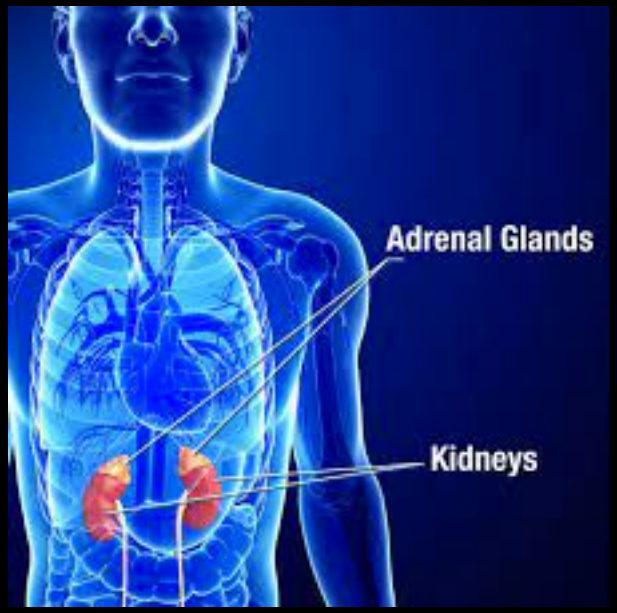
- Medical/Surgical Interventions

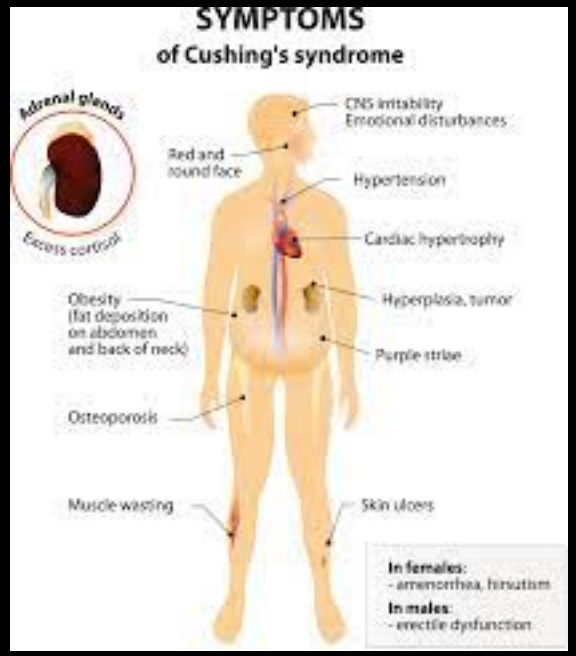
  - ❖ Transphenoidal surgery in patients with pituitary neoplasia.
  - ❖ Medications including long-acting dopamine agonists (cabergoline & bromocriptine)
  - ❖ Somatostatin analogs (octreotide) 50-100mcg SC/IV TID; titrate to serum GH < 5.
  - ❖ GH receptor agonists (pegvisomant)10-30mg SC daily; based IGF levels.



MRI Brain
Pituitary Tumor

Addison’s Disease
Cushing Syndrome





Overview/Addison's Disease

- Etiology: Primary/Secondary
  - ❖ Due to failure of adrenal cortex to produce & synthesize sufficient amounts of glucocorticoid hormones.
  - ❖ Primary adrenal insufficiency: AKA "Addisonian crisis". Many causes including autoimmune process, idiopathic, infectious process including adrenal TB, toxoplasmosis, histoplasmosis, human immunodeficency syndrome.
  - ❖ Secondary adrenal insufficiency: AKA "Acute Adrenal crisis". Multiple causes including rapid or abrupt discontinuation of exogenous steroids. Adrenalectomy, adrenal hemorrhage/necrosis, pituitary surgery, pituitary trauma, RT.

- Epidemiology
  - ❖ Primary: Affects 93-140/1,000,000 worldwide; 4.7-6.2/1,000,000 in white populations.
  - ❖ Secondary: Affects 150-280/1,000,000 worldwide; more common due to use of exogenous corticosteroids.
  - ❖ Women affected more than men.
  - ❖ Occurs 3rd – 5th decade.

Pathophysiology

Cortical Hormones	Function	Dysfunction
Glucocorticoids (cortisol)	CHO, Protein & Lipid metabolism; anti-inflammatory properties.	Hypoglycemia
Mineralocorticoid (aldosterone)	Renin-angiotensin mechanism- increases Na absorption & K excretion.	Loss of Na & H_2O leading to hypovolemia & dehydration.

Medullary Hormones	Function	
Epinephrine/Norepinephrine	Fight or flight response.	
	Insulin antagonist.	
Adrenal Androgens	**Function**	**Dysfunction**
	In women responsible for development of secondary sex characteristics.	Lack of libido, axillary & pubic hair loss.

- Due to hypofunction of Adrenal gland leading to decreased secretion of vital hormones.

Data Assessment

- Subjective
  - ❖ Primary: Fatigue, lethargy, muscle weakness, decreased labido, anorexia/weight loss, n/v, abdominal pain
  - ❖ Acute/Secondary: Confusion, agitation, symptoms of hypoglycemia, symptoms of circulatory collapse.

- Objective
  - ❖ Signs of circulatory collapse including hypotension, hypovolemia.
  - ❖ Labs: hypoglycemia, hyponatremia, hyperkalemia
  - ❖ Weight loss, increased pigmentation of the skin.
- Diagnostics
  - ❖ Serum cortisol levels (early morning 6-9am), serum Na & K.
  - ❖ 24 hr urine cortisol excretion (urinary 17-hydroxycorticosteroids.
  - ❖ ACTH Stimulation test

Addison's disease

Adrenal glands not produce sufficient steroid hormones

Adrenal crisis:
- fever;
- syncope;
- convulsions;
- hypoglycemia;
- hyponatremia;
- severe vomiting and diarrhea.

Skin
Hyperpigmentation

Low blood pressure
Weakness
Weight loss

Gastrointestinal
Nausea
Diarrhea
Vomiting
Constipation
Abdominal pain

Skin
Vitiligo

Management

- Medical

Acute adrenal insufficiency:

1. Includes fluid volume replacement, correction of hypoglycemia, hyponatremia, hyperkalemia if present.
2. Stress dose hydrocortisone 100mg IV q8hrs.
3. Maintenance: Hydrocortisone (glucocorticoid replacement) 12-25 mg/m^2/day or fludrocortisone (mineralocorticoid
   replacement) 0.05-0.3 mg orally once daily.

Primary adrenal insufficiency :

1. Maintenance: Hydrocortisone (glucocorticoid replacement) 12-25 mg/m^2/day or fludrocortisone (mineralocorticoid replacement) 0.05-0.3 mg orally daily.
2. Dehydroenpiandrosterone (androgen replacement) 20-50mg in woman daily

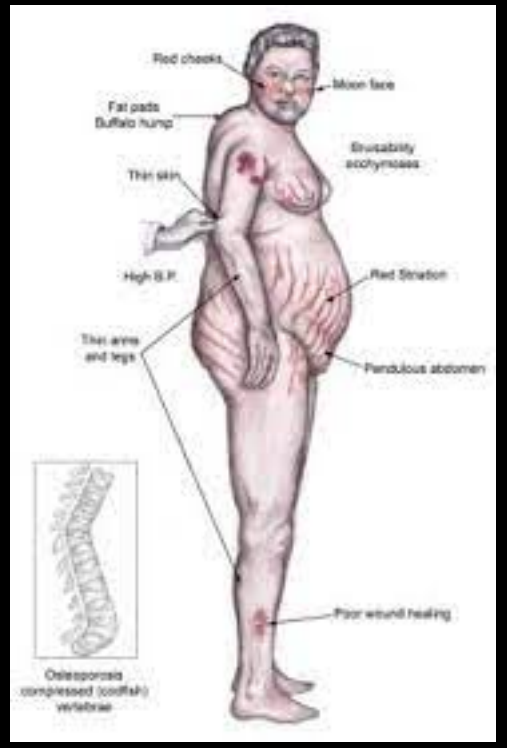
Complications

- Acute Adrenal Insufficiency
  - ❖ Life threatening event if not recognized & managed emergently.
  - ❖ Occurs in individuals with Addison's disease who experience trauma, any type of physiologic stress.
  - ❖ Signs & Symptoms include dehydration, hypotension, hypoglycemia, hyponatremia, hyperkalemia & abdominal pain.
  - ❖ Treatment: IV infusion 0.9% Normal Saline to reverse hypovolemia. Administration of dexamethasone or prednisone to reverse glucocorticoid deficiency (Physiologic stress dose: 200-300mg hydrocortisone daily).

Overview/Cushing's Syndrome

- Etiology

  - Due to prolonged multiorgan exposure to free circulating glucocorticoid.
  - Primary Cushing Syndrome: Tumors arising from adrenal cortex; adenomas or carcinomas.
  - Secondary Cushing Syndrome: excessive cortisol production from adrenal hyperplasia due to excessive corticotropin production from either the pituitary gland (basophil adenomas, chromophobe adenomas); or outside the pituitary gland including oat-cell CA of the lung or pancreatic islet cell CA
  - Iatrogenic Cushing Syndrome: long-term exogenous glucocorticoid therapy.



- Epidemiology

  - Higher incidence in women than men.
  - Occurs in 2nd-4th decades of life in women

Pathophysiology

- Excessive cortisol production

  - Gluconeogenesis & glycogenolysis due to excessive production of circulating blood glucose.
  - Increased catabolism of protein.
  - Fat metabolism alteration.
  - Normal inflammatory response of body diminishes.
  - Abnormal secretion of both serum Na with associated water retention.
  - Androgen secretion increases.
  - Individual observed to have altered emotional response.

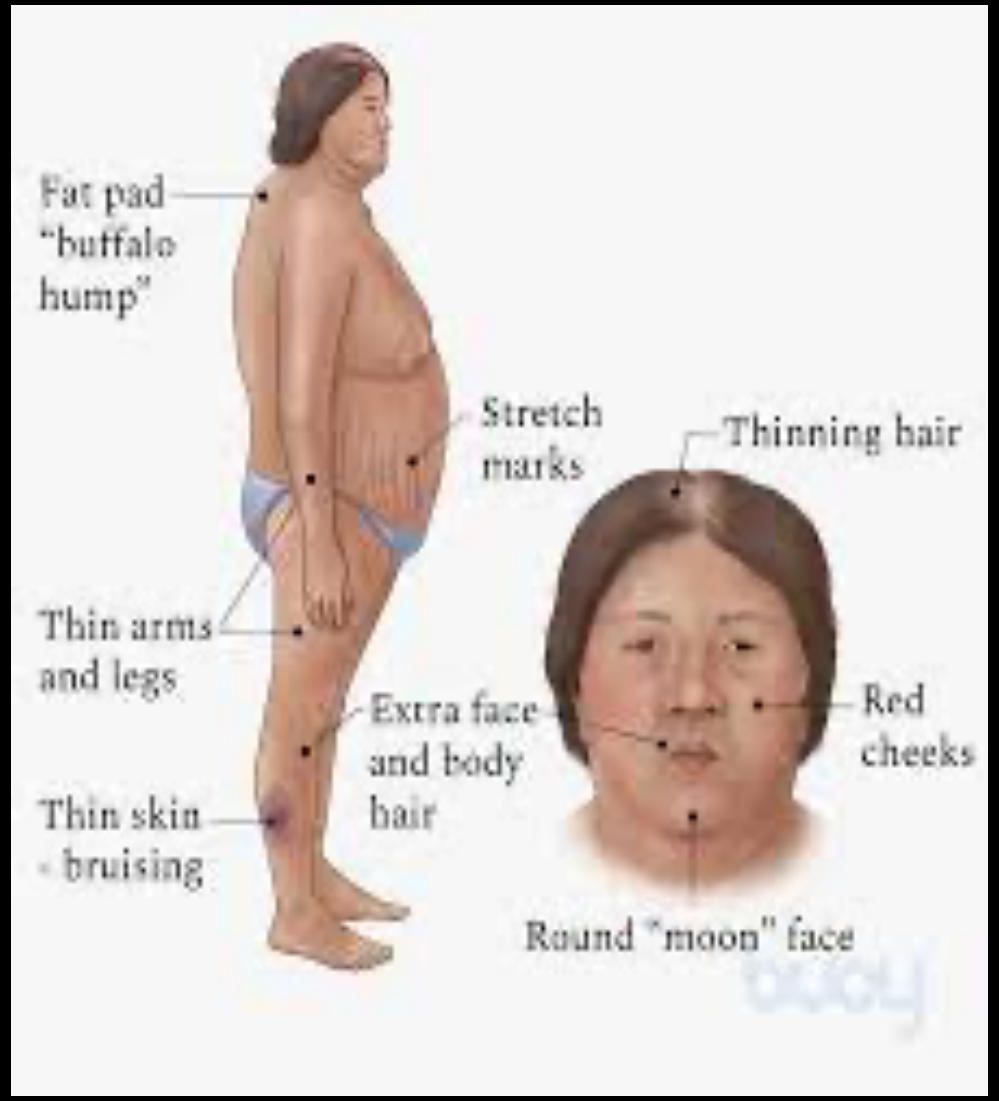
Data Assessment

- Subjective

  - Patient may complain of generalized weakness, 2^0 muscle atrophy.
  - Complaints of decreased or diminished sex drive, changes in menstrual cycle.
  - Emotional lability; complaints of fatigue.
  - Frequent infections.

- Objective

  - Thinning of scalp hair; in women hirsutism.
  - Evidence of hyperglycemia.
  - Muscle atrophy/wasting.
  - Evidence of osteoporosis; frequent fractures.
  - Hypokalemia may result in cardiac arrhythmias & renal disorders.
  - Physical features may include moon shape face, increased dorsocervical fat pad-giving “buffalo-hump” appearance. Limbs may be disproportionally thinner than torso
  - Skin changes including development of abdominal & breast straie, acne.
  - Decreased cognition



Classic features
Cushing's Syndrome

Management

- Diagnostic Work-Up
  - Assess for hypercortisolism (elevated salivary, serum and urine cortisol levels.
  - Assess for serum ACTH levels.
  - Serum electrolytes, glucose.
  - Dexamethasone suppression test.
  - Abdominal imaging to rule out adrenal mass.
  - MRI imaging of brain to rule out pituitary mass

- Medical/Surgical
  - Transphenoidal hypophysectomy
  - Adrenalectomy
  - Radiation therapy for pituitary tumor in lieu of surgery.
  - Medications that inhibit adrenocorticotropic hormone secretion or antagonize glucocorticoid action.

Thank you for attending

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