***Pathology***

***Pituitary gland:***

***Anterior pituitary:***

Notes:

1. Diseases related to anterior pituitary gland causes either hyperpituitarism OR hypopituitarism
* Hyperpituitarism (excessive secretion of one or more of hormones) is caused by:
1. **Adenoma** (few adenoma are bilineage, such as GH +prolactin) b)hyperplasia c)carcinoma
* Hupopituitarism (deficiency of one or more of pituitary hormones) is caused by :
1. **Non functional adenoma** b) congenital hypoplasia c)**ischemia(Sheehan syndrome)**

 d) surgery e) radiation f) inflammation h)**bone disease (osteopetrosis)**

2. pituitary adenomas can be:

a) functional OR non functional. Non functional adenomas can be silent (non secretory) OR hormone negative (non synthesizing)

b) sporadic (97%) OR syndromic (3% multiple endocrine neoplasia)

c) <1 cm (micro adenoma) OR >1cm called (macro adenoma)

3. pituitary tumors(adenoma) cause :damage to optic nerve (temporal hemianopsia) / increased intracranial pressure (headache ,nausea , and vomit)

4. pituitary adenomas have a **mutant G-protein** with autonomous activity.

***Pituitary adenomas***

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| adenoma | Type(functioning/Non functioning) | Size (macro/micro)adenoma | Onset of symptoms | symptoms | notes |
| Prolactinoma(most common adenoma) | functional | **Premenopausal women: micro adenoma****Men & postmenopausal women: macro adenoma** | Premenopausal women: earlyPostmenopausal women& men: late | Amenorrhea /galactorrhea/loss of libido /infertility | **HyperProlactinoma (excessive prolactin secretion)can be caused by conditions other than prolactin secreting pituitary adenoma such as the stalk effect which causes interruption in the hypothalamic pituitary axis.** |
| Gh-producing tumors (second most common adenoma) | Functional (secretes little amounts of GH) | Macro adenoma  | late | -Before the epiphyses is closed(childhood):Gigantism-After the epiphyses is closed (adult hood): acromegally-Also develops hypertension/diabetes/heart failure. | GH stimulates the secretion of Insulin Like Growth factor from the liver |
| Corticotroph cell adenoma  | functional | Micro adenoma | early | -**Cushing disease( bilateral adrenal enlargement)****-Hyperpigmentation (ACTH & MSH share precursor)**  | **Corticotroph adenoma may develop after bilateral adrenolectomy and this condition is called Nelson syndrome** |
| Gonadotoph adenoma(rare) | Functional but the amount of hormones secreted is very minimal and thus isnot responsible for the symptoms appearing.so the symtomps are related to mass effect | macroadenoma | late | \_ \_ \_ \_ \_ | \_ \_ \_ \_ \_ |
| Thyrotroph adenoma(rare) | Functional but the amount of hormones secreted is very minimal and thus is not responsible for the symptoms appearing. so symptoms are related to mass effect. But in some cases it is responsible of hyperthyroidism  | macroadenoma | late | \_ \_ \_ \_ \_ | \_ \_ \_ \_ \_ |

***Posterior pituitary*** (secretes ADH & oxyticin):

 \*ADH acts on the kidney to promote water reabsorbtion.

1) **ADH deficiency (diabetes inspidius) is:** 2) **Excessive ADH (syndrome of inappropriate ADH) is:**

 **Caused by: head trauma, tumors, and surgery** **Caused by: paraneoplastic syndrome (small cell carcinoma of the lung)**

 **Symptoms: polyurae, dilute urine, hypernatremia)** **Symptoms: hyponatremia, and brain edema.**

Thyroid gland:

Notes:

Thyrotoxicosis: hypermetabolic state caused by increased T3 & T4 in the blood

 Caused by : 1) **increased function of thyroid gland (hyperthyroidism)**

 2) Exogenous source of thyroid hormones

 3) Thyroiditis (physical damage to thyroid gland)

 Symptoms: heat intolerance, excessive sweating, soft flushed warm skin, nervousness, increased sympathetic stimulation,

 Tremor, irritability, GI: diarrhea & malabsorbtion, Cardiac : arrhythmia & palpitation, ocular: lid lag & wide staring

 Eyes, **thyroid storm: life threatening** , **apathetic hyper thyroidism : asymptomatic in elderly.**

 **Exopthalmus (hyperthyroidism eyes): most common in GRAVE’s disease.**

Hypothyroidism: low level of T3 in blood.

 Symptoms: 1) **cretinism:** developing in infants or early childhood .manifested by : impaired skeletal and CNS development ,

 Mental retardation, short stature, coarse face, protruding tongue. Caused by: low iodine, inborn enzyme errors.

 2) **Myxedema:** adult onset disease manifested by: slow mental process, apathy, cold intolerance, constipation,

 Anemia, bradycardia, heart failure.

 **Diffuse and multi nodular goiter:**

**-A goiter is an enlargement of the thyroid gland. It reflects impaired synthesis of thyroid hormone which leads to a compensatory enlargement of the gland in order to produce higher amounts of hormones.**

**Goiters can be endemic or sporadic:**

1. **endemic goiter: 10% or more of the population has goiter ,in areas where soil , water and food contain little iodine (Himalaya)**
2. **sporadic goiter: idiopathic mostly. Could be caused by ingestion of substances interfering with thyroid hormone synthesis such as excessive calcium intake, cabbage, cauliflower or enzymatic deficiency.**

**-it is commonly caused by iodine deficiency which leads to compensatory rise in TSH causing hypertrophy & hyperplasia of follicular epithelium (diffuse goiter)- similar to Grave’s disease- so that thyroid hormones level can get back to normal (euthyroid).**

**When euthyroid level is reached , TSH decreases , follicular epithelium becomes small and flat , with predominance of colloid forming ( colloid nodule or colloid goiter) with repeated attacks of hyperplasia and hypertrophy (if the underlying cause of hypo thyroidism persist) ,variable proliferation will occur ,fibrosis , hemorrhage ,cyctic degeneration ,calcification goiter is irregular forming (multinodular goiter).**

**Notes:**

**\*\*all diffuse goiter which develop at early stages will eventually progress to multinodular goiter.**

**\*\*normally: follicular epithelial cells are heterogeneous in response to TSH.**

**\*\*both mono clonal and poly clonal nodules are present.**

**\*\*some nodules in multinodular goiter become dominant and secrete excess hormone (toxic multinodular goiter) which causes Plummer syndrome.**

**-clinically: the main complaint is a mass in the neck causing : cosmetic problems, stridor, dysphagia, compression of vessels.**

 **Plummer syndrome: when toxic multinodular goiter produces hyperthyroidism (no ocular disease)**

 **Some patients have hypothyroidism.**

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| **NON neoplastic thyroid gland diseases** |
| Disease  | Predominance (Male/ Female) | Hypo/ hyper thyroidism | Presence of GOITER(painful OR painless) | pathogenesis | Genetic predisposition | morphology | Clinical manifestation |
| Chronic lymphocytic (Hashimoto) thyroiditis-most common cause of hypothyroidism- | female | **hypo** | Present, painless  | -**autoimmune** disease-depletion of epithelial cells ,replaced by lymphocytes and plasma cells.-autoreactive CD4+T-LYMPHOCYTES against normal thyroid antigens.-autoreactive CD4 T-LYMPHOCYTES produce INF-Y-recruitment of macrophages ,CD8+T-lymphocutes and plasma cells  | Family history,HLA-DR3,HLA-DR5 | Grossly:- **diffuse homogeneous enlargement of thyroid gland** -intact capsule, not adherent to adjacent structures.Microscopically:-infilteration with B -lymphocytes(**germinal centers**), plasma cells ,T-lymphocytes and macrophages-atrophic follicular epithelium with metaplastic changes to large, pink cuboidal cells called **HURTHLE cells or OXYFIL cells**-with time fibrosis and atrophy | -initial transient phase of thyrotoxicosis followed by progressive hypothyroidism-risk of **beta cell lymphoma but not thyroid carcinoma** |
| Subacute granulomatous (De Quervian) thyroiditis | female | **hyper** | Present, painful | -**viral infection or post viral inflammation**  | \_ \_ \_ \_ \_ \_  | Grossly: **enlargement of the thyroid gland, could be asymmetrical, not adherent** Microscopically:-disruption of thyroid follicle.-infiltration by granulocytes, lymphocytes, plasma cells ad macrophages.-**extravasated colloid initiates foreign body reaction, forming granulomas.** | Fever, malaise, transient hyperthyroidism, leukocytosis-self limited  |
| Subacute lymphoctic thyroiditis | female | **hyper** | No or minimal goiter | -**autoimmune****-develops in post partum women and returns in future pregnancies** | \_ \_ \_ \_ \_ \_ | Microscopically:-lymphocytic infiltration, **germinal centers, but no HURTHLE cells**  | \_ \_ \_ \_ \_ \_ \_ \_ \_ |
| Riedel thyroiditis  | \_ \_ \_ \_ \_ \_ \_ \_ | \_ \_ \_ \_ \_ \_ \_  | Adherent hard goiter | -unknown etiology, **maybe autoimmune**- **Progressive fibrosis of thyroid and surrounding structures****-fibrosis in other organs (retroperitonium)** | \_ \_ \_ \_ \_ \_ | Microscopically:**Thick fibrous bands with minimal follicles** | Adherent hard enlargement (goiter) of the thyroid gland |
| Palpitation thyroiditis | \_ \_ \_ \_ \_ \_ \_ \_  | **Unlike De -Quervian thyroiditis there is no abnormality in thyroid function**  | \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ | Vigorous palpitation of the gland | \_ \_ \_ \_ \_ \_  | Microscopically: Multifocal follicular disruption with chronic inflammatory cells and occasional giant cell formation |  |
| Grave’s disease Most common cause of hyper thyroidism | females | **Hyper with transient episodes of hypo** | present | -**autoimmune**-break in CD4 tolerance against normal thyroid antigens which activates B-lymphocytes to secrete auto anti bodies -antibodies are:1) **thyroid stimulating immunoglobulin (TSH) specific : stimulates secretion of thyroid hormones.****2)thyroid growth stimulating immunoglobulin (TGI): stimulates proliferation of follicular epithelium.**3)TSH-binding inhibitor immunoglobulin (TBII): prevents TSH binding to its receptor and stimulates proliferation of follicular cells. Other forms inhibit thyroid function.4)anti thyroglobulin, anti thyroid peroxidase. | Family history, HLA-DR3 & B8 | Grossly:-Diffuse goiter,soft, non adherent -intact capsuleMicroscopically:-hyperplastic follicular epithelial cells (tall. Columnar crowded, small papillae, project into follicular lumen, lack of fibrovascular cores)-colloid is pale, scalloped margins-lymphoid infiltrate, **germinal centers.** \*\*\*in the skin it causes:Edema, lymphocyte infiltration and glycosaminoglycans deposition (infiltrative dermatopathy)\*\*\*in the eye (infiltrative opthalmopathy) is caused by: infilteration by inflammatory cells /inflammatory edema/accumulation of extracellular matrix/increased fat cells. | Triad: **thyrotoxicosis/ infiltrative opthalmopathy / localized infiltrative dermatopathy ( peritibial Myxedema)** Notes: -Exopthalmus is caused by infiltrative opthalmopathy-Exopthalmus is persistent even with treartment.  |

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| **Neoplastic thyroid gland diseases** |
| Type of neoplasia | location | Benign/ Malignant | Pathogenisis/Genetic mutations | morphology |
| Follicular adenomaMostly non functional (cold nodule) but rarely can be functional and cause hyperthyroidism | Follicular epithelium | benign | -activating mutations in TSH receptor or alpha subunit (of G protein) causing over production of cAMP which causes cell growth and mitosis.-20% of cases have RAS (a G protein) mutations. | Grossly:-difficult to distinguish from hyperplastic nodule or carcinoma.-solitary, well demarcated mass with intact ,thin capsule (not present in hyperplastic nodule).Microscopically:-uniform follicles contain colloid distinct from the rest of the thyroid. Cells are uniform.-if follicular cells show HURTHLE cell changes it is called HURTHLE cell adenoma.-atypia might be present but does not mean malignancy.-no capsular invasion, if capsular invasion is present it is follicular carcinoma.  |
| Papillary carcinoma (most common of thyroid carcinomas) Note: it is an indolent disease with 95% of 10 years survival. | Follicular epithelium | malignant | -history of previous ionizing radiation.-mutations activating mitogen activating protein (MAP) kinase signaling pathway.-1/3 have BRAF gene mutations which activate MAP.-20% have mutations in RET gene rearrangement (tyrosine kinase receptor) creating novel gene (ret/PTC)which activate RET and MAP.-10% have neurotropic tyrosine kinase receptor 1(NTRK1) mutations.  | Grossly:-painless mass in the neck.-solitary or multiple.-well circumscribed, sometimes encapsulated.-commonly associated with lymph nodes metastasis but this does not affect prognosis.Microscopically: Special nuclear features:-optically clear nuclei, called ground glass or orphan ANNIE eyes.-nuclear groves (psaudoinclusions)-papillary architecture.-concentric calcification (psammoma bodies),cysts are common. |
| Follicular carcinoma (second most common thyroid carcinoma) | Follicular epithelium  | malignant | -associated with iodine deficiency -RAS mutations in 50% of cases. | Microscopically:-Normal looking follicles ,may show HURTHLE cells-invasion to capsule or lymphatics. |
| Medullary carcinoma (nueroendocrine neoplasm ) | Parafollicular cells  | malignant | -80% are sporadic at old age.-20% are familial (familial medullary thyroid carcinoma or multiple endocrine neoplasia) at young age, aggressive disease.-RET gene mutations. | Grossly:-solitary tumor (sporadic ) or multiple (familial)Microscopically:-secretes amyloid (derived from calcitonin) ,positive for Congo red stain.Amyloid appears as homogeneous extracellular material.-C-cell hyperplasia in non tumerous areas.Electron microscopy:Membrane bound granules containing calcitonin.Note: there is an increased blood level of calcitonin but there is no hypocalcemia.  |
| Anaplastic carcinoma | Follicular epithelium  | Malignant (very aggressive), rapid growth and death within a year. | -history of multi nodular goiter or papillary thyroid carcinoma (PTC)Note: occurs at old age | Microscopically:-cells are large, epithelioid or spindle, pleomorphic. |

Notes:

\*\*thyroid carcinomas are rare.

\*\*thyroid carcinomas are mostly occurring at young adulthood , with female predominance (estrogen receptor)

\*\*old and pediatric cases might occur if cases are exposed to risk factor such as radiation.

***Done by: Russole Emad***

***Good luck!!!***