ANTERIOR PITUITARY ADENOMA

- The most common pituitary tumor
- Can be functional or non-functional
- Called microadenoma if size ≤1cm, very common, incidental finding, can be functioning
- Called macroadenoma if size >1cm
- Large non-functional adenoma causes hypopituitarism
- May cause symptoms related to mass-effect (increased intracranial pressure, optic nerve compression, hydrocephalus)
- Histologic morphology does not correlate with functional status

LACTOTROPH ADENOMA (PROLACTINOMA)

- The most common functioning pituitary adenoma (30%)
- Dystrophic calcification is common (pituitary stones)
- Causes amenorrhea, galactorrhea, infertility and loss of libido
- Symptoms are less obvious in men and post-menopausal women (more chance to reach large size)
- High prolactin causes endothelial dysfunction and insulin resistance (cardiovascular diseases)
- Diagnosis: very high level of serum prolactin
- Mild increase in serum prolactin may accompany other types of pituitary adenoma or hypothalamic diseases due to interference with the normal inhibitory control of dopamine causing lactotroph hyperplasia
- Chronic renal failure: decreased clearance of prolactin
- **Primary hypothyroidism: high TRH increases prolactin secretion**
- **Drugs blocking dopamine receptor (anti-depressants)**

SOMATOTROPH ADENOMA

- Growth-hormone secreting adenoma
- Second most common functional PA, non-functional SA is rare
- Commonly reach large size
- Gigantism in children (long bones)
- Acromegaly in adults (skin, soft tissue, viscera)
- Also causes diabetes, hypertension, GI cancer, gonadal dysfunction
- May accompany lactrotroph adenoma (mammosomatotroph)
- Microscopy: densely and sparsely granulated variants (the latter is more aggressive and non-responsive to somatostatin therapy)

CORTICOTROPH ADENOMA

- Functional adenomas produces ACTH causing hypersecretion of adrenal cortisol causing Cushing Disease
- Commonly microadenoma, densely or sparsely granulated
- Crooke cell adenoma: another variant, showing ring-like cytokeratin protein inside the cells, clinically aggressive
- Proopiomelanocortin (POMC): precursor of ACTH, stains positive for PAS stain
- Cushing Syndrome: central obesity, hypertension, hyperglycemia
- Nelson syndrome: secondary to bilateral adrenalectomy, progressive enlargement of PA causing tumor effect, skin hyperpigmentation (POMC - melanotropin)

GONADOTROPH ADENOMA

- Usually produces small amounts LH and FSH hormones (silent)
- Most symptoms are related to mass-effect or hypopituitarism (impaired secretion of LH loss of libido, amenorrhea)
- Rarely secrete large amount of LH/FSH macroorchidism, hyperspermia, ovarian hyperstimulation

THYROTROPH ADENOMA

- TSH-producing adenoma, uncommon (<1% of PA)
- Rare causes of hyperthyroidism

PLURIHORMONAL ADENOMA

- Secrete multiple hormones, clinically aggressive

NULL CELL AENOMA

* Do not express any markers of hormones, not differentiated

PITUITARY APOPLEXY

- Rare condition that complicates pituitary adenoma
- Sudden hemorrhage in pituitary gland causing acute enlargement and damage
- Symptoms of increased intracranial pressure (severe headache, nausea, vomiting, visual disturbance)
- Symptoms of hypopituitarism
- Loss of ACTH causes hypotension and hypoglycemia (fatal)
- Critical condition, neurosurgical intervention
- A similar but milder condition results from pituitary infarction secondary to ischemia (Sheehan syndrome), occurs in post partum hemorrhage

PITUITARY CARCINOMA

- Rare, <1% of pituitary tumors
- Most are functional (prolactin or ACTH-secretion is most common)
- Differentiated from PA by metastasis

PITUITARY BLASTOMA

- Malignant pituitary tumor, arises in children <2 years
- Morphologically undifferentiated cells (blastema)
- Cushing syndrome is common

DISEASES OF POSTERIOR PITUITARY GLAND

Diabetes Insipidus (DI)

- Deficiency in anti-diuretic hormone (ADH), called “central DI”
- Results in inability of kidneys to reabsorb fluids (polyurea, polydipsia, dehydration)
- Results from head trauma (including brain surgery), hypothalamic diseases (tumors, inflammation)
- Can be genetic: mutation in arginine vasoprossin or its receptor
- Nephrogenic DI: kidney is unresponsive to ADH (similar symptoms)

SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

- Results in over-reabsorption of water in kidneys (oligourea, hyponatremia, cerebral edema, brain dysfunction)
- Although total body fluid is increased, blood volume remains normal, no peripheral edema
- Usually caused by a paraneoplastic syndrome (small cell carcinoma of lung)
- Also caused by drugs, CNS inflammation or trauma

CRANIOPHARYNGIOMA

- Suprasellar tumor, arises from the vestigial epithelium of Rathke pouch
- Slowly growing tumor
- Bimodal age distribution (children 5-15, old >65 years)
- Presentation: hypopituitarism (Dwarfism in children), DI, tumor effect (in adults)
- Adamantinomatous CPh: squamous cell with keratin, common in children, also shows dystrophic calcification, may produce cyst or becomes inflammatory producing “machine oil” material
- Papillary CPh: squamous cells show papillae formation, no keratin, no cyst, no calcification seen in adults

DIABETES MELLITUS

- Group of metabolic disorders results in chronic hyperglycemia
- Multi-organ damage (kidneys, retina, cardiovascular)
- Very common
- Increased morbidity and mortality
- Risk factors: family history, life-style, obesity

TYPE-1 DIABETES

- 5% of all DM cases
- Autoimmune destruction of pancreatic β-cells
- Commonly affects children and adolescents
- Symptoms tend to appear rapidly, although the cell damage takes time
- Associated with HLA-DR3, DR-4, DQ8
- Polymorphism in CTLA4 and PTPN22 genes (similar to autoimmune thyroiditis)
- Environmental factor: virus epitopes, only 50% of monozygotic twins share DM-1
- Failure of self-tolerance in T-cells for islet antigens
- Other less common causes DM: chronic pancreatitis, pancreatic carcinoma, cystic fibrosis, hemochromatosis, infections by cytomegalovirus, coxsackie virus, congenital rubella, systemic amyloidosis

TYPE-2 DIABETES

- >90% of DM cases
- Peripheral resistance to insulin
- Inadequate response by β-cells to overcome this resistance
- Patients are commonly obese, adults, insidious onset
- Impaired function of incretins (peptides secreted form small intestine following glucose feeding, promotes secretion of insulin from B-cells)
- Genetic factors: 90% concordance rate in identical twins, 10x risk in first degree relative. Genes related to adipose-tissue distribution in body, B-cell function and obesity
- Environmental factors: central obesity is most important, then sedentary life-style, circadian-disruption (sleep disorder)

- B-cell dysfunction results from:
- Excess free fatty acids (due to increased activity of lipase enzyme in adipose tissue)
- Hyperglycemia: toxic effect
- Amyloid deposition in B-cells: seen in 90% of long-standing DM-2
- Genetic susceptibility

OTHER CAUSES OF TYPE-2 DIABETES

- Endocrinopathies: Cushing syndrome, acromegaly, hyperthyroidism, pheochromocytoma, glucagonoma
- Drugs: steroids, β-agonists, phenytoin, thiazide
- Certain syndromes: Down, Turner
- Gestational diabetes (5% of pregnant women, due to increased steroid hormones)

MONOGENIC FORMS OF DM

- Maturity-onset diabetes of the young (MODY)
- Resemble DM-2
- Results from germline loss of function mutation in glucokinase (GCK) genes, affects glucose metabolism and insulin secretion
- Rarely: mutation is insulin-receptor synthesis, binding or activity, associated with hyperinsulinemia and skin pigmentation

HYPERGLYCEMIA EFFECT ON TISSUE

- **(1) Advanced glycation end products (AGE)**: non-enzymatic glucose addition to molecules results in activation of AGE signaling, resulting in cytokines and growth factors release causing vascular proliferation (retinopathy) and basement membrane deposition (nephropathy), release of reactive oxygen species, procoagulant activity and proliferation of vascular smooth muscle cells
- **(2) Activation of protein kinase C**: results in activation of plasminogen activator inhibitor-1 (procoagulant effect)
- **(3) Oxidative stress and disturbance in polyol pathways**: occurs in tissues that do not require insulin to take glucose (nerves, lenses, kidneys, blood vessels): hyperglycemia results in increased intracellular glucose that ends up with depletion of NADPH, making these cells susceptible to oxidative stress

CLINICAL PRESENTATION

- Polyurea, polydipsia (osmotic effect), polyphagia, weight loss (catabolic effect)
- Chronic systemic complications results from chronic hyperglycemia
- Macrovascular: myocardial infarction, stroke, lower limb ischemia
- Microvascular: retinopathy, nephropathy, neuropathy
- Varies among patients
- Tight control of blood glucose level prevents complications

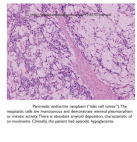
DIABETIC KETOACIDOSIS

- Mostly seen in type-1 DM
- Failure to take insulin, stress, infections, trauma
- May occur in type-2 DM with severe stress (release of epinephrin which blocks residual insulin and stimulates release of glucagon).
- Severe hyperglycemia causes osmotic diuresis and dehydration
- Insulin deficiency promotes ketone body synthesis, when severe and accompanied by dehydration, results in metabolic acidosis (fatigue, nausea, vomiting, abdominal pain, difficult breathing, fruity odor, loss of consciousness, coma.

HYPEROSMOLAR HYPERGLYCEMIC STATE

- Affects DM-2
- Osmotic diuresis results in dehydration, if not corrected (stroke, infections, no enough water drinking), results in mental status dysfunction and coma. No ketons are produced.

HYPERINSULINISM (INSULINOMA)



Pancreatic endocrine neoplasm ("islet cell tumor"). The neoplastic cells are monotonous and demonstrate minimal pleomorphism or mitotic activity.There is abundant amyloid deposition,characteristic of an insulinoma. Clinically,the patient had episodic hypoglycemia.

- Most common pancreatic endocrine neoplasm
- Hyperinsulinemia results in hypoglycemic episodes (usually mild)
- In severe forms causes confusion and loss of consciousness
- Mostly single tumor, benign behavior (90%)
- Microscopically appears as giant islets, contain amyloid
- Islet-cell hyperplasia is seen in newborns of diabetic mothers (cause serious hypoglycemia after birth, transient)

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

- Arises in pancreas or duodenum
- Causes severe peptic ulcer, jejunal ulcer
- 50% are malignant
- 25% of cases appear as a part of MEN-1 syndrome (multifocal)

HYPERCORTISOLISM

- AKA Cushing syndrome
- Can be exogenous (iatrogenic) or endogenous (less common)
- Endogenous causes are divided into ACTH-dependent and independent

ACTH-secreting PA is the most common cause of endogenous hypercortisolism (60%), AKA Cushing Disease, more common in women, young adults, functional microadenoma
- Adrenal glands show bilateral nodular hyperplasia

Ectopic ACTH production:

- 5-10% of endogenous Cushing syndrome cases
- More common in men, middle age
- Small cell carcinoma of lung, carcinoid tumor, medullary carcinoma of thyroid, pancreatic neuroendocrine tumors
- In some cases, ectopic production of CRH
- Again, bilateral adrenal nodular hyperplasia
- Pathologic changes is less prominent than pituitary cause, secondary to poor prognosis of accompanied cancer

Primary adrenal adenoma

- 10-20% of ACTH-independent cases
- Low ACTH level (negative feedback on pituitary)
- PRKAR1A genetic mutation
- The other adrenal gland is atrophic
- More common in women
- Adrenal gland is <30 g
- Non-functional adrenal adenoma is more common

Adrenal carcinoma

- 5-7% of ACTH-independent cases
- Very large size of adrenal glands
- Produces very high level of cortisol
- Genetic mutations in: activation of beta-catenin (CTNNB1), inactivation of TP53, MEN1 and PRKAR1A
- The adrenal gland is > 200 g
- The other adrenal gland is atrophic

Primary adrenal hyperplasia:

- Independent of ACTH
- Rare
- Shows bilateral adrenal cortical hyperplasia, nodules are larger than 1 cm
- Familial disease: inherited mutation in the tumor suppressor gene: armadillo repeat containing 5 (ARMC5)
- Sporadic disease: 50% show ARNC5 mutation, others show ectopic production of G-protein coupled hormone receptors (similar action of ACTH)
- Syndromic disease: McCune Albright syndrome, germline activating mutation in GNAS, produces excessive cAMP ? multisystemic disease

Micronodular bilateral adrenal hyperplasia


- ACTH-independent
- Small nodules (<1 cm)
- Two variants: primary pigmented nodular adrenocortical disease or Carney complex (multisystemic disease of endocrine and non-endocrine neoplasms)
- Both variants harbor mutation in cAMP-dependent protein kinase (PRKAR1A gene), producing excessive cAMP

CLINICAL SYMPTOMS OF CUSHING DISEASE

- Hypertension
- Central obesity, moon face, buffalo hump
- Proximal muscle weakness (atrophy)
- Hyperglycemia, glucoseurea, polyurea, polydipsia
- Bone resorption (osteoporosis)
- Collagen degradation (thin skin, easy bruise, poor wound healing, striation
- Hisrutism
- Menstrual abnormalities
- Immune suppression
- Mental and psychotic disturbances

PRIMARY HYPERALDOSTERONISM

- Chronic excessive production of aldosterone
- Patients develop hypertension, hypokalemia, suppression of renin-angiotensin system and decreased renin activity
- Primary hyperaldosteronism is caused by one of three diseases:

(1) Bilateral idiopathic hyperaldosteronism (60%):

- Bilateral nodular hyperplasia of zona glomerulosa cells
- Most commonly sporadic, old patients, mild hypertension
- Germline mutation in KCNJ5
- Morphology: diffuse enlargement of the adrenal gland, sometime subtle and not obvious

(2) Adrenocortical neoplasm (35%):

- Functional adenoma or carcinoma
- Conn syndrome: adrenal adenoma that secretes aldosterone only, more common in middle-age women
- 50% harbor KCNJ5 mutation, which encodes potassium channel on zona granulosa cells (called GIRK4 protein), mutant protein allows influx of sodium and activation of aldosterone synthase enzyme
- Morphology: adenoma is small, more common on left adrenal, buried within the gland (difficult to be seen in radiology), yellow in color and resemble fasciculata cells. Spironolactone bodies: intracellular eosinophilic material following treatment with antihypertensive drugs
- The other adrenal gland is NOT atrophic

(3) Familial hyperaldosteronism (5%)

- Four subtypes
- FH-1 is the most common (AKA glucocorticoid-remediable aldosteronism), mutation in CYP11B2 (encoding aldosterone synthase), becomes sensitive to ACTH
- The other four subtypes are rare

SECONDARY HYPERALDOSTERONISM

- Activation of renin-angiotensin system
- Increased level of plasma renin, occurs in:
- Decreased renal perfusion (renal artery stenosis or arteriolar nephrosclerosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (estrogen-induced)

ADRENOGENITAL SYNDROMES

- Normally, the adrenal glands secrete dehydroepiandrosterone and androstenedione which converts to testosterone
- Secretion is ACTH-dependent
- Adrenocortical neoplasm associated with virilization: carcinoma is more common than adenoma, can be pure or mixed with hypercortisolism

CONGENITAL ADRENAL HYPERPLASIA

- Group of autosomal recessive disorders
- Deficiency in enzymes responsible for synthesizing cortisol
- Steroid precursors accumulate and shifts to synthesis of androgens resulting in virilization
- Maybe associated with deficiency in aldosterone synthesis, too
- 21-hydroxylase deficiency: the most common deficiency (90%), mutation in CYP21A1 gene, variable degree of deficiency, results in either:
- Salt wasting syndrome: associated with deficiency in aldosterone, cortisol and catecholeamine synthesis, appears in utero or shortly after birth (hyponatremia, hypokalemia, hypotension, cardiovascular collapse, virilization in females)
- Simple virilization: no salt wasting, genital ambiguity
- Late-onset adrenal virilism: common, partial enzyme deficiency: hirsutism, acne, irregular menses
- Morphology: bilateral nodular hyperplasia of adrenals, brown, hyperplasia of pituitary corticotroph cells

ADRENOCORTICAL INSUFFICIENCY

- Primary: adrenal failure (acute or chronic)
- Secondary: ACTH deficiency
- Primary acute adrenocortical insufficiency: sudden withdrawal of exogenous steroids, massive adrenal hemorrhage (newborns, difficult delivery and hypoxia), coagulopathy
- Waterhouse-Friderichsen syndrome: overwhelming bacterial infection (classically occurs in Neisseria meningitidis), direct injury to adrenal vessels resulting in hemorrhage and damage to adrenals

PRIMARY CHRONIC ADRENOCORTICAL INSUFFICIENCY

- Called Addison disease
- Uncommon
- Progressive destruction of adrenal cortex
- Symptoms appear after 90% damage to adrenocortical tissue ▪ Causes: autoimmune inflammation, infections (HIV, TB)

PHEOCHROMOCYTOMA

- Tumor of adrenal medulla (chromaffin cells)
- Secretes catecholamines, results in hypertension
- 10% bilateral, 10% biologically malignant, 10% not associated with hypertension, 10% arises in extra-adrenal sites (carotid body, called paraganglioma), 10% familial (early-life onset)
- Genetic mutations in growth-factor receptor pathway genes (RET, NF1) or increased activity of hypoxia-induced transcription factors (HIF-1α, HIF-2α)
- Morphology: variable size, may show necrosis, bleeding, incubation with potassium dichromate produces dark brown color (chromaffin)
- Histology: small nests of cells separated by supporting sustentacular cells (zellballen)
- Malignancy is determined by the presence of metastasis, not histology