Endocrine Pathology II
Parathyroid Glands

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Educational Goals and Objectives

- Define and describe the following terms:
  - Hyperparathyroidism
  - Hypercalcemia
  - Parathyroid adenoma
  - Parathyroid hyperplasia
  - Parathyroid carcinoma
  - Hypoparathyroidism
  - Pseudohypoparathyroidism
  - Chvostek's sign
  - Trousseau's sign
- Compare and contrast the pathogenesis, pathology and clinical manifestations of primary and secondary hyperparathyroidism.
- Describe the pathogenesis and clinical manifestations of hypoparathyroidism.
- Reading Assignment: Robbins Pathologic Basis of Disease (Cotran, Kumar, Robbins), 10th Ed. Chapter 20, pp.769-771.

Anatomy and Embryology

- Derived from pharyngeal pouches
- 10% of individuals have 2 or 3 glands
- Each weighs 35-40 mg
- Could be found in the carotid sheath, thymus, and anterior mediastinum
Parathyroid gland - Histology

- Chief cells predominate and contain glycogen, produce PTH.
- Oxyphil cells in small clusters, packed with mitochondria.
- Fat, increases with age up to 25 years, occupies 30% of adult gland.

Parathyroid gland - histology

- Chief cells – polygonal, with central round uniform nuclei.
- Cytoplasm of chief cells may appear clear “water clear cells” due to glycogen lakes (glycogen is washed off during processing leaving clear spaces).
- Oxyphil cells found in groups all over the gland – pink granular cytoplasm due to tightly packed mitochondria.

Function of parathyroid

- PTH production is controlled by free (ionized) calcium in the bloodstream.
- PTH, 84 amino acids linear polypeptide with the biologic activity residing in the 34 residues at the amino terminus.
- Decreased levels of free calcium in the blood causes secretion of parathormone (PTH).
**Parathyroid Hormone (PTH)**

- Activates osteoclasts by mobilizing calcium from bone
- ↑ renal tubular reabsorption
- ↑ conversion of vitamin D to active form
- ↓ serum phosphate by ↑ urinary excretion
- Augments GI calcium absorption
- **Net effect is increase in serum calcium levels which in turn exerts a negative feedback effect on secretion of PTH**

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**Diseases of the Parathyroid**

- Hyperparathyroidism
  - Primary
  - Secondary
  - Tertiary
- Hypoparathyroidism

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**Primary Hyperparathyroidism**

- Usually a disease of adults ~ 50 years
- Male: Female = 1:4
- Annual incidence is 25/100,000 in the US
- May be sporadic or familial
- Frequency of parathyroid lesions underlying hyperparathyroidism is
  - Parathyroid Adenoma 85-95%
  - Primary Hyperplasia (diffuse or nodular) 5-10%
  - Parathyroid Carcinoma ~1%
Familial primary hyperparathyroidism

- Genetic syndromes associated with familial hyperparathyroidism are:
  1. MEN 1 - inactivation of MEN 1 gene on chromosome 11q13 (tumor suppressor gene)
  2. MEN 2A - activating mutation of RET (tyrosine kinase receptor) gene on chromosome 10q
  3. Familial hypocalciuric hypercalcemia – autosomal dominant disorder due to mutation in parathyroid calcium-sensing receptor gene (CASR) on chromosome 3q

Parathyroid adenoma
- Almost always solitary
- 0.5 to 5.0 grams in weight
- Radionuclide scan demonstrates increased uptake in left inferior parathyroid gland
- The other glands show normal uptake
- In parathyroid hyperplasia more than one gland will show abnormal uptake

Parathyroid Adenoma
- Sheets or nests of chief cells or oxyphil cells
- Encapsulated lesion with compressed normal rim of parathyroid at the periphery
Parathyroid adenoma

- Sheets of chief cells, may sometimes have nests of oxyphil cells
- Rarely the entire adenoma is composed of oxyphil cells and is called oxyphil adenoma
- Mitotic figures are rare
- May find bizarre and pleomorphic nuclei within the adenoma (endocrine atypia) which represents degenerative change and is not a criteria for malignancy
- No/conspicuous fat

Parathyroid hyperplasia

- Involves 2-4 glands
- Combined weight of all four < 1.00 gm
- Microscopically diffuse or multinodular chief cell hyperplasia is most common
- Fat is inconspicuous within the foci of hyperplasia

Parathyroid carcinoma

- Solitary mass, may exceed 10 gm
- May be circumscribed lesions or clearly invasive neoplasms
Parathyroid carcinoma

Cells resemble normal parathyroid cells and are arranged in trabeculae or nodules with dense fibrous capsule with intervening fibrous bands

Diagnosis: local invasion of surrounding tissue and metastasis

Morphologic changes in other organs in hyperparathyroidism

- Skeletal changes – increased bone resorption due to increased activity of osteoclasts accompanied by increased osteoblastic activity
- Resulting bone has thinned out defective trabeculae somewhat like osteoporosis
- Osteitis fibrosa cystica – thinned bony cortex with marrow containing fibrous tissue, hemorrhage and cyst formation
- Brown tumor – collections of osteoclasts, reactive giant cells and hemorrhagic debris forming masses that simulate tumor

Kidney changes

- Formation of stones (nephrolithiasis)
- Calcification of renal interstitium and tubules (nephrocalcinosis)
- Metastatic calcification in organs like stomach, liver, myocardium or blood vessels

Morphologic changes in other organs in hyperparathyroidism
Primary Hyperparathyroidism
Clinical Manifestations

- May be asymptomatic and identified by hypercalcemia on routine chemistry profile
- Symptomatic and identified by the constellation of findings
- "painful bones, renal stones, abdominal groans and psychic moans"
- Symptoms may be due to elevated PTH (bone and kidneys) or due to hypercalcemia

Hypercalcemia

- Hypercalcemia is one of the changes caused by elevated PTH
- Hypercalcemia is also routinely caused by malignancy like that of lung, breast, head and neck and multiple myeloma
- Malignancy is the most common cause of clinically apparent hypercalcemia while primary hyperparathyroidism is the most common cause of incidental hypercalcemia
Causes of Hypercalcemia

**Elevated PTH**
- **Hyperparathyroidism**
  - Primary
  - Secondary
  - Tertiary
- Familial hypocalciuric hypercalcemia (FHH)

**Decreased PTH**
- Hypercalcemia of malignancy
- Vitamin D toxicity
- Immobilization
- Thiazide diuretics
- Granulomatous disease (Sarcoidosis)

Hypercalcemia of Malignancy

- Osteolytic metastases: tumor \(\Rightarrow\) cytokines \(\Rightarrow\) local osteolysis, by promoting maturation of osteoclasts
- Tumors may not metastasize to the bone but hypercalcemia is part of paraneoplastic syndrome, primary tumor releases PTH-related protein (PTHrP) causing bone resorption
- Prognosis is poor, as patients present at advanced stage

Secondary Hyperparathyroidism

- Process of chronic depression or decrease in calcium that causes compensatory over activity of the parathyroid glands
- Etiology: Renal failure most common –
  - Renal insufficiency causes decreased phosphate excretion causing hyperphosphatemia which in turn decreases serum calcium leading to parathyroid stimulation
  - Depressed renal mass leads to deficiency of \(\alpha\)-1 hydroxylase causing deficiency of active Vitamin D leading to less absorption of calcium from GI tract and eventually parathyroid stimulation
- Other etiologies: decreased dietary Ca, steatorrhea and Vit D def
- Pathologic findings in the parathyroids is similar to primary parathyroid hyperplasia
Secondary Hyperparathyroidism
Clinical manifestations

- Chronic renal failure and skeletal changes (renal osteodystrophy)
  - Skeletal changes not as severe as in primary hyperparathyroidism
- Vascular calcifications may cause significant ischemic damage to skin known as calciphylaxis

Tertiary hyperparathyroidism

- Minority of patients - autonomous hyperparathyroidism with symptomatic hypercalcemia
- Parathyroidectomy necessary for controlling symptoms

Hypoparathyroidism

- Far less common than hyperparathyroidism
- Decreased PTH and hypocalcemia

- Etiology:
  - Surgically induced – may be removed inadvertently during thyroidectomy, lymph node dissection (mistaken as lymph nodes) or a larger portion of parathyroid removed during treatment of hyperparathyroidism
  - Autoimmune hypoparathyroidism – often associated with mucocutaneous candidiasis and adrenal insufficiency (Autoimmune polyendocrine syndrome1, APS1)
  - Autosomal dominant hypoparathyroidism – gain of function mutation in Calcium sensing receptor gene (CASR) – leads to hypercalciuria and hypocalcemia
  - Familial isolated hyperparathyroidism – rare disorder due to mutation in the gene encoding PTH precursor peptide
  - Congenital absence of parathyroid - as part of DiGeorge syndrome or 22q11 syndrome
Hypoparathyroidism
Clinical manifestations

- Tetany: neuromuscular irritability – symptoms include circumoral numbness, paraesthesias (tingling) of distal extremities, carpopedal spasm, laryngospasm and seizures
  - Chvostek sign – tap along the course of facial nerve and observe the contractions of the muscles of mouth, eye or nose
  - Trousseau sign – occlude the circulation in the forearm by tying a blood pressure cuff, observe the carpal spasms
- Mental status changes – emotional instability, anxiety, depression, confusion, hallucinations and frank psychosis

- Intracranial manifestations – calcifications of basal ganglia, Parkinson like movement disorders and increased intracranial pressure with papilledema
- Ocular disease – cataract formation
- Cardiovascular manifestation – conduction defect with prolonged QT interval
- Dental abnormalities – specially evident if hypocalcemia present during early development – dental hypoplasia, failure of eruption, defective enamel and root formation and carious teeth

Pseudohypoparathyroidism

- Rare disease due to end organ resistance to the actions of PTH
- Increased or normal PTH with hypocalcemia
A 38-year-old man sees his physician because of abdominal pain, nausea, and constipation for the past 3 days. On physical examination he has no palpable abdominal masses and bowel sounds are present. His lungs are clear to auscultation. He has a heart rate of 80 with an irregular rhythm. An EKG demonstrates a shortened QT(corrected) interval and a prolonged PR interval. He has a stool positive for occult blood. Upper GI endoscopy reveals multiple 1 cm diameter shallow ulcerations of the gastric antrum. Which of the following laboratory test findings is most likely to be present in this man?

A) Thyroid peroxidase antibody of 4 IU/mL (ref <9 IU/ML)
B) Serum calcium of 12.4 mg/dL (ref 8.5 -10.5 mg/dl)
C) Blood glucose of 225 mg/dL (ref 70- 100 mg/dl)
D) Total serum thyroxine of 21 ug/dL (ref 5-11 ug/dl)
E) Plasma cortisol of 45 ug/dL at 8 am (ref 4-22 ug/dl)

A 50 year old man diagnosed with papillary thyroid carcinoma underwent total thyroidectomy. Within a few hours of surgery the patient complained of tingling of his fingers. Which of the following laboratory tests should be ordered to direct further therapy for this patient.

A. serum TSH
B. serum parathormone
C. serum ionized calcium
D. serum Total T4