ENDOCRINE PATHOLOGY II
Parathyroid Gland

I. Introduction

A. Derived from pharyngeal pouches.
B. Usually four glands found in close proximity of the thyroid
C. 10% of individuals have only 2 or 3 glands
D. Yellow-brown, ovoid, encapsulated nodule weighing 35-40 mg. histologically composed of:
   1. Predominantly chief cells which secrete parathyroid hormone (PTH) and contain glycogen, water clear cells which are chief cells with glycogen lakes
   2. Oxyphil cells packed with mitochondria
   3. Stromal fat /adipose tissue comprising a maximum of 30% of gland, increases up to 25 years and then plateaus
E. PTH- 84 amino acid long linear peptide with the activity residing in 34 amino acids at the N terminal. Activity controlled by level of free (ionized) calcium in the bloodstream. Decreased levels of free calcium stimulate the synthesis and secretion of PTH
   1. Mobilization of calcium from bone (osteoclasts)
   2. Increase renal tubular absorption/retention
   3. Increase conversion of vitamin D to its active form in kidney
   4. Decrease serum phosphate by increasing urinary phosphate excretion
   5. Increase GI tract absorption
F. PTH receptor is a G protein coupled receptor.
G. Hypercalcemia is a one of the number of changes induced by elevated levels of PTH. Malignancy is the most common cause of symptomatic hypercalcemia whereas primary hyperthyroidism usually causes asymptomatic hypercalcemia
H. Hypercalcemia of Malignancy
   1. Osteolytic metastases and local release of cytokines (breast cancer and multiple myeloma)
   2. Paraneoplastic syndromes: Primary tumor producing PTH-related protein (PTHrP) activating the PTH receptors resulting in bone reabsorption (squamous cell carcinoma of the lung, renal cancer, bladder cancer, and ovarian cancer). Also called “humoral hypercalcemia of malignancy”
Hyperparathyroidism - may be primary, secondary or rarely tertiary.

II. Primary Hyperparathyroidism

- Pathologic process of the parathyroid gland causing excess secretion of parathyroid hormone (PTH) leading to hypercalcemia.
- Disease of adults with M:F ratio of 1:3
- More than 95% of cases caused by sporadic adenomas or hyperplasia with less than 55 being associated with genetic syndromes

Etiology/Pathology

1. Parathyroid Adenoma 75-80%
   a. Macroscopic: generally solitary nodule that expands and compresses normal parathyroid at the periphery; encapsulated weighing between 0.5 and 5.0 gms.
   b. Microscopic: sheets of chief cells, nests of oxyphilic cells; with few or no fat cells

3. Primary Hyperplasia 10-15%
   a. Macroscopic: generally 2-4 glands involved with a combined weight of all four glands <1.00 gm; no capsule
   b. Microscopic: chief cells predominate with foci of oxyphilic cells; occasional, but reduced fat cells

4. Parathyroid Carcinoma <5%
   a. Macroscopic: may exceed 10 grams
   b. Microscopic: dense fibrous capsule with intervening fibrous bands
   c. Diagnosis: presence of local invasion and metastasis

Genetic syndromes associated with familial primary hyperparathyroidism

1. Multiple endocrine neoplasia 1 (MEN-1) – tumor suppressor gene on chromosome 11q13
2. Multiple endocrine neoplasia 2 (MEN-2) – tyrosine kinase receptor RET on chromosome 10q.
3. Familial hypocalciuric hypercalcemia (FHH) - autosomal dominant disorder due to decreased sensitivity to extracellular calcium due to mutations in calcium sensing receptor gene (CASR) on chromosome 3q

Established molecular defects in sporadic adenomas

- Parathyroid adenoma 1 (PRAD 1): inversion chromosome with over expression of cyclin d-1 resulting in cell proliferation; seen in 20% of adenomas
- MEN 1: Homozygous loss of a suppressor gene on chromosome 11q13 (MEN 1); seen in 20% of sporadic adenomas and most of patients with familial MEN I Syndrome
**Clinical Manifestations**

1. May be asymptomatic, or present with vague complaints
2. Signs and symptoms reflect the combined effects of increased PTH secretion and hypercalcemia
   - bone disease
   - nephrolithiasis
   - gastrointestinal disturbances including constipation, nausea, peptic ulcers, pancreatitis and gallstones
   - depression, lethargy and weakness
   - weakness and fatigue
   - aortic and/or mitral valve calcifications

The abnormalities most directly related to hyperparathyroidism are nephrolithiasis and bone disease whereas the others may be attributed to hypercalcemia.

### III. Secondary Hyperparathyroidism

Condition in which a pathologic process in another organ (not the Parathyroid) causes compensatory overactivity of the parathyroid glands (secondary hyperplasia) with excess secretion of PTH.

#### Etiology/Pathogenesis
- This syndrome occurs most often in patients with renal failure;
  - Mechanism postulated to be: renal failure causing retention of phosphorus leading to direct depression of serum calcium levels leading in turn to stimulation of parathyroid gland activity.
- Inadequate dietary intake of Calcium
- Steatorrhoea & vitamin D deficiency
- Pathology is similar to primary parathyroid hyperplasia

#### Clinical Manifestations
1. Reflects chronic renal failure and skeletal changes which are referred to as renal osteodystrophy (osteitis fibrosa cystica/osteomalacia)
2. Vascular calcifications: ischemic damage to skin and other organs (calciphylaxis)

### IV. Tertiary Hyperparathyroidism

- Definition: Autonomous (or Independent) and excessive gland activity
- Develops from a minority of patients with secondary hyperparathyroidism that is long-standing
- May require parathyroidectomy
V. **Hypoparathyroidism**

- A functional abnormality characterized by decreased PTH and hypocalcemia.

*Etiology/Pathogenesis:*
- Surgically induced hypoparathyroidism with inadvertent removal of all parathyroid glands
- Congenital absence of all glands in developmental anomalies like 22q11.2 syndrome
- Familial hypoparathyroidism which is often associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency; syndrome known as autoimmune polyendocrine syndrome type 1 caused by mutations in the autoimmune regulator (AIRE) gene
- Idiopathic or autoimmune hypoparathyroidism with auto antibodies directed against Calcium sensing receptor (CASR)

*Clinical Manifestations*

1. Decreased ionized calcium in serum
2. Tetany - neuromuscular irritability or excitability
   - A: Chvostek’s sign - facial nerve
   - B: Trousseau sign - carpal spasm
3. Mental irritability or instability with anxiety or depression to psychoses
4. Cataract formation
5. Conduction defect: prolongation of QT interval on the EKG
6. Dental abnormalities
7. Intracranial manifestations with calcification of basal ganglia, parkinsonian like movement disorders and increased intracranial pressure with papilledema

VI. **Pseudohypoparathyroidism**

A. Rare disease as a result of end organ resistance to PTH.

B. There are abnormalities or defects in the PTH receptor complex.

C. Hypocalcemia with compensatory increased parathyroid activity.