

DISORDERS OF THE PARATHYROID GLANDS

- Maintenance of calcium, phosphate and magnesium homeostasis is under the influence of two polypeptide hormones; parathyroid hormone(PTH), and calcitonin (CT), as well as a sterol hormone, 1,25 dihydroxy cholecalciferol (1,25 (OH) $2 D 3$).
- These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on intestine, kidneys, and bones.

- The PTH acts directly on the bones and kidneys and indirectly on the intestine through its effect on the synthesis of $1,25(\text{OH})_2\text{D}_3$.
- Its production is regulated by the concentration of serum ionized calcium.
- Lowering of the serum calcium levels will induce an increased rate of parathyroid hormone secretion

- Calcitonin is released by the “C” cells (parafollicular cells in the thyroid gland) in response to small increases in plasma ionic calcium.
- It acts on the kidney and bones to restore the level of calcium to just below a normal set point which in turn inhibits secretion of the hormone.
- Calcitonin is therefore the physiological antagonist of PTH.
- The two hormones act in concert to maintain normal concentration of calcium ion in the extracellular fluid.

Primary hyperparathyroidism

- Primary hyperparathyroidism is due to excessive production of PTH by one or more of hyperfunctioning parathyroid glands.
- This leads to hypercalcemia which fails to inhibit the gland activity in the normal manner.
- The cause of primary hyperparathyroidism is unknown.
- A genetic factor may be involved. The clonal origin of most parathyroid adenomas suggests a defect at the level of the gene controlling the regulation and/or expression of parathyroid hormone.

- The incidence of the disease increases dramatically after the age of 50 and it is 2-4 folds more common in women.
- A single adenoma occurs in about 80% of patients with primary hyperparathyroidism.
- Four glands hyperplasia account for 15-20% of cases.
- A parathyroid carcinoma could be the etiology in a rare incidence of less than 1%.

Clinical Features

- The two major sites of potential complications are the bones and the kidneys.
- The kidneys may have renal stones (nephrolithiasis) or diffuse deposition of calcium- phosphate complexes in the parenchyma (nephrocalcinosis).
- Nowadays such complications are seen less commonly and around 20% of patients or less show such complications

- In skeleton a condition called osteitis fibrosa cystica could occur with subperiosteal resorption of the distal phalanges, distal tapering of the clavicles, a “salt and pepper” appearance of the skull as well as bone cysts and brown tumors of the long bones.
- Such overt bone disease even though typical of primary hyperparathyroidism is very rarely encountered
- Nowadays almost 90% of diagnosed cases in the developed countries are picked up by routine screening for calcium level using the new automated machines.

- Other symptoms include muscle weakness, easy fatigability, peptic ulcer disease, pancreatitis, hypertension, gout and pseudogout as well as anemia and depression have been associated with primary hyperparathyroidism.

Diagnosis

- The presence of established hypercalcemia in more than one serum measurement accompanied by elevated immunoreactive PTH is characteristic (iPTH)
- Serum phosphate is usually low but may be normal.
- Hypercalcemia is common and blood alkaline phosphatase (of bone origin) and the urinary hydroxyproline concentrations are commonly elevated when the bones are involved.
- Nephrogenous cAMP is elevated in about 80% of patients but the test is rarely used because of technical difficulties

Other Diagnostic tests

- The hypercalcemia of non-parathyroid origin e.g., vitamin D intoxication, sarcoidosis and lymphoproliferative syndromes generally respond to the administration of prednisolone in a dose of 40-60 mg daily for 10 days by a decrease in serum calcium level. The Glucocorticoid suppression test:
- The response is unusual in hypercalcemia secondary to primary hyperparathyroidism and ectopic PTH production.
- A positive test result i.e. significant decrease in serum calcium is a contraindication to neck exploration and signals the need for investigation for a non-parathyroid cause of the hypercalcemia.

Radiograph

- Plain X-ray of hands can be diagnostic showing subperiosteal bone resorption usually on the radial surface of the distal phalanx with distal phalangeal tufting as well as cysts formation and generalized osteopenia
- Ultrasonography, MRI, CT, Thallium 201 – Technetium 99m scan (subtraction study) for Pre-operative localization of the abnormal parathyroid gland(s):

Treatment

- A large proportion of patients have “biochemical” hyperparathyroidism but with prolonged follow up they progress to overt clinical presentation.
- Resection of the parathyroid lesion is curative with recurrences observed mainly in the multiple glandular disease.

Medical Treatment

- Medical Treatment of the hypercalcemia. In acute severe forms the mainstay of therapy is adequate hydration with saline and forced diuresis by diuretics to increase the urinary excretion of calcium rapidly along with sodium and prevent its reabsorption by the renal tubules.
- Glucocorticoids –In hypercalcemia associated the hematological malignant neoplasms
- Mithramycin –A toxic antibiotics which inhibit bone resorption and is used in hematological and solid neoplasms causing hypercalcemia.

- Calcitonin –Also inhibit osteoclast activity and prevent bone resorption
- Bisphosphonates –They are given intravenously or orally to prevent bone resorption.
- Phosphate –Oral phosphate can be used as an anti hypercalcemic agent and is commonly used as a temporary measure during diagnostic workup.
- Estrogen –It also decrease bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy

Surgery

- Surgical treatment should be considered in all cases with established diagnosis of primary hyperparathyroidism.
- During surgery the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by the removal of enlarged parathyroid
- Complications Deterioration of renal function, Metabolic disturbance e.g. hypomagnesemia, pancreatitis, gout or pseudogout

Secondary hyperparathyroidism

- An increase in PTH secretion which is adaptive and unrelated to intrinsic disease of the parathyroid glands is called secondary hyperparathyroidism.
- This is due to chronic stimulation of the parathyroid glands by a chronic decrease in the ionic calcium level in the blood
- Major causes of chronic hypocalcemia other than hypoparathyroidism
 1. Dietary deficiency of vitamin D or calcium.
 2. Decreased intestinal absorption of vitamin D or calcium due to primary small bowel disease, short bowel syndrome, and post-gastrectomy syndrome.
 3. Drugs that cause rickets or osteomalacia such as phenytoin, phenobarbital, cholestyramine, and laxative.

4. States of tissue resistance to vitamin D
5. Excessive intake of inorganic phosphate compounds
6. Pseudohypoparathyroidism
7. Severe hypomagnesemia
8. Chronic renal failure

Hypoparathyroidism

Deficient secretion of PTH which manifests itself biochemically by hypocalcemia, hyperphosphatemia, diminished or absent circulating PTH and clinically the symptoms of neuromuscular hyperactivity.

Surgical hypoparathyroidism

- The commonest –After anterior neck exploration for thyroidectomy,
- Abnormal parathyroid gland removal,
- Excision of a neck lesion.
- It could be due to the removal of the parathyroid glands or due to interruption of blood supply to the glands.

Idiopathic hypoparathyroidism

- A form occurring at an early age (genetic origin) with autosomal recessive mode of transmission
- “multiple endocrine deficiency – autoimmune-candidiasis (MEDAC) syndrome”
 - “Juvenile familial endocrinopathy”
 - “Hypoparathyroidism – Addison's disease – mucocutaneous candidiasis (HAM) syndrome”
- Circulating antibodies for the parathyroid glands and the adrenals are frequently present.
- Other associated disease: Pernicious anemia, Ovarian failure, Autoimmune thyroiditis, Diabetes mellitus
- The late onset form occurs sporadically without circulating glandular autoantibodies

Functional hypoparathyroidism

In patients who has chronic hypomagnesaemia of various causes. – Magnesium is necessary for the PTH release from the glands and also for the peripheral action of the PTH

Clinical Features:

A . Neuromuscular –The rate of decrease in serum calcium is the major determinant for the development of neuromuscular complications. – When nerves are exposed to low levels of calcium they show abnormal neuronal function which may include

- Decrease threshold of excitation,
- Repetitive response to a single stimulus and
- Rarely continuous activity.

A . Neuromuscular

- Parathesia
- Tetany
- Hyperventilation
- Adrenergic symptoms
- Convulsion (More common in young people and it can take the form of either generalized tetany followed by prolonged tonic spasms or the typical epileptiform seizures.
- Signs of latent tetany, Chvostek sign, Trousseau sign, Extrapyrarnidal signs (due to basal ganglia calcification)

B . Other clinical manifestation

1. Posterior lenticular cataract

2. Cardiac manifestation: Prolonged QT interval in the ECG
Resistance to digitalis Hypotension Refractory heart failure with cardiomegaly can occur

3. Dental Manifestation Abnormal enamel formation with delayed or absent dental eruption and defective dental root formation.

4. Malabsorption syndrome Presumably secondary to decreased calcium level and may lead to steatorrhea with long standing untreated disease.

Diagnosis:

- In the absence of renal failure the presence of hypocalcemia with hyperphosphatasemia is virtually diagnostic of hypoparathyroidism.
- Undetectable serum PTH confirms the diagnosis or it can be detectable if the assay is very sensitive.

Treatment:

- The mainstay of treatment is a combination of oral calcium with pharmacological doses of vitamin D or its potent analogues.
- Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level.

Emergency Treatment for Hypocalcaemic Tetany:

- Calcium should be given parenterally till adequate serum calcium level is obtained and then vitamin D supplementation with oral calcium should be initiated.

Emergency Treatment for Hypocalcaemia

- In patients with hyperparathyroidism and severe bone disease who undergo successful parathyroidectomy, hypocalcaemia may be severe and parenteral calcium infusion with later supplementation with oral calcium and vitamin D. (Hungry bone syndrome)

Pseudohypoparathyroidism and Pseudo pseudohypoparathyroidism

- A rare familial disorders with target tissue resistance to PTH.
- There is hypocalcemia, hyperphosphatemia, with increased parathyroid gland function.
- There is also a variety of congenital defects in the growth and development of skeleton including: Short stature, Short metacarpal and metatarsal bones
- In pseudo pseudohypoparathyroidism they have the developmental defects without the biochemical abnormalities