THE PARATHYROID GLANDS

-The four parathyroid glands lie behind the lobes of the thyroid. The parathyroid chief cells respond directly to changes in calcium concentrations via the calcium-sensing receptor located on the surface of parathyroid chief cells.

- PTH is a single-chain polypeptide of 84 amino acids that is secreted in response .to a fall in plasma ionised calcium concentration

- PTH has direct effects that promote reabsorption of calcium from renal tubules and bone. PTH also has indirect effects, mediated by increasing renal conversion of 25-hydroxycholecalciferol (i.e. 25-hydroxy-vitamin D) to the more potent hormone 1,25-dihydroxycholecalciferol, which results in increased calcium absorption from food.

--99% of total body calcium is in bone,.

-About 50% of circulating calcium is bound to organic ions such as citrate or phosphate and to proteins. Total calcium measurements need to be corrected if the serum albumin is low, by adjusting the value for calcium upwards by 0.1 mmol/l (0.4 mg/dl) for each 5 g/l reduction in albumin below 40 g/l.

HYPERCALCAEMIA

Hypercalcaemia is one of the most common biochemical abnormalities and is often detected during routine biochemical analysis in asymptomatic patients., it can present with chronic symptoms, and occasionally patients present as an acute emergency with severe hypercalcaemia and dehydration

--CAUSES OF HYPERCALCAEMIA

-With normal or elevated (i.e. inappropriate) PTH levels

-Primary or tertiary hyperparathyroidism

- Lithium-induced hyperparathyroidism

-Familial hypocalciuric hypercalcaemia

HYPERCALCAEMIA

--With low (i.e. suppressed) PTH levels

-Malignancy (e.g. lung, breast, renal, ovarian, colonic (and thyroid carcinoma, lymphoma, multiple myeloma

-Elevated 1,25(OH)2 vitamin D (e.g. vitamin D intoxication,

sarcoidosis, HIVThyrotoxicosis--

Paget's disease with immobilisation-----

-Milk-alkali syndrome

-Thiazide diuretics

-Glucocorticoid deficiency

--primary hyperparathyroidism and malignant hypercalcaemia are by far the most common causes.

--Familial hypocalciuric hypercalcaemia (FHH) is a rare but important. This autosomal dominant disorder is caused by an inactivating mutation in the calcium-sensing receptor, which reduces the ability of the parathyroid gland to 'sense' ionised calcium concentrations. As a result, higher than normal calcium levels are required to suppress PTH secretion.

Marginal elevations in serum calcium levels are typically observed in affected individuals, with PTH concentrations that are 'inappropriately' at the upper end of the normal range, or even slightly elevated.

In addition, a reduced sensitivity of calcium-sensing receptors in the kidney tubules leads to increased calcium reabsorption and hypocalciuria. An individual with FHH is almost always asymptomatic and without complications, but may end up having an unnecessary (and ineffective) parathyroidectomy if misdiagnosed as having primary hyperparathyroidism.

--Lithium may also cause hyperparathyroidism by reducing the sensitivity of the calcium-sensing receptor

Clinical assessment

- -Symptoms and signs of hypercalcaemia include polyuria and polydipsia, renal colic, lethargy, anorexia, nausea, dyspepsia and peptic ulceration, constipation, depression, drowsiness and impaired cognition.
- --Patients with malignant hypercalcaemia can have a rapid onset of symptoms .and may have clinical features that help to localise the tumour
- --Patients with primary hyperparathyroidism may have a chronic, non-specific history. Their symptoms are described by the adage 'bones, stones and abdominal groans'. However, about 50% of patients with primary hyperparathyroidism are asymptomatic.
- --patients present with renal calculi (5% of first stone formers and 15% of recurrent stone formers have primary hyperparathyroidism).
- --Hypertension is common in hyperparathyroidism. -
- -Parathyroid tumours are almost never palpable.
- -A family history of hypercalcaemia raises the possibility of FHH or MEN

Investigations

-Low plasma phosphate and elevated alkaline phosphatase support a diagnosis of primary hyperparathyroidism or malignancy.

-High plasma phosphate and alkaline phosphatase accompanied by renal impairment suggest tertiary hyperparathyroidism.

-The most discriminant investigation is the measurement of PTH using a specific immunoradiometric assay.

-If PTH is normal or elevated and urinary calcium is elevated, then hyperparathyroidism is confirmed.

- Low urine calcium excretion indicates likely FHH

TREATMENT OF SEVERE HYPERCALCAEMIA

---Rehydration with normal saline

To replace as much as a 4-6 l deficit

May need monitoring with central venous pressure in old age or renal impairment

--Bisphosphonates

e.g. disodium pamidronate 90 mg i.v. over 4 hours

Causes a fall in calcium which is maximal at 2-3 days and lasts a few weeks

--Additional rapid therapy may be required in very ill patients

. Forced diuresis with saline and furosemide

. Glucocorticoids, e.g. prednisolone 40 mg daily

.Calcitonin

.Haemodialysis

Treat the cause

HYPERPARATHYROIDISM

It is customary to distinguish three categories of hyperparathyroidism,

--primary hyperparathyroidism there is autonomous secretion of PTH, usually by a single parathyroid adenoma varying in size from a few millimetres to several centimetres in diameter.

--Secondary hyperparathyroidism is present when there is increased PTH secretion to compensate for prolonged hypocalcaemia and is associated with hyperplasia of all parathyroid tissue. Its effect is to restore serum calcium levels at the expense of the stores of calcium in bone.

--tertiary hyperparathyroidism, a very small proportion of cases of secondary hyperparathyroidism, continuous stimulation of the parathyroids results in adenoma formation and autonomous PTH .secretion.

-Primary hyperparathyroidism is the most common of the parathyroid disorders

. It is two to three times more common in women than men

-and 90% of patients are over 50 years of age.

-hyperparathyroid bone disease is now rare due to earlier diagnosis and treatment.

---- Osteitis fibrosa results from increased bone resorption by osteoclasts with fibrous replacement in the lacunae. This may present as bone pain and tenderness, fracture and deformity. ----

-----Chondrocalcinosis is due to deposition of calcium pyrophosphate crystals within articular cartilage. It typically affects the menisci at the knees and can result in secondary degenerative arthritis or predispose to attacks of acute pseudogout

-There are characteristic changes on plain X-rays.

-- In the early stages there is demineralisation, with subperiosteal erosions and terminal resorption in the phalanges . A 'pepper-pot' appearance may be seen on .lateral X-rays of the skull. .

-Reduced bone mineral density is now the most common skeletal manifestation of hyperparathyroidism by DEXA .scanning

- imaging to locate the adenoma or differentiate adenomas from hyperplasia has traditionally not been necessary.

In over 90% of patients an experienced surgeon will locate the adenoma without difficulty.

Management

-Hypercalcaemia in patients with primary hyperparathyroidism responds less well to glucocorticoids and bisphosphonates than in those with malignancy.

-Urgent neck surgery is occasionally required, but strenuous attempts should be made to replace fluid deficits and lower the serum calcium concentration

-Surgery is indicated for young patients < 50 years) and those with clear-cut symptoms or documented complications such as peptic ulceration, renal stones, renal impairment or osteopenia.

-large number of patients have only vague symptoms or are asymptomatic. They can be reviewed every 6-12 months and should be encouraged to maintain a high oral fluid intake to avoid renal stones

-Drugs that enhance the sensitivity of the calcium-sensing receptor (calcimimetics) are being developed and, in the future, may offer an alternative to surgery in hyperparathyroidism

HYPOCALCAEMIA

-The most common cause of hypocalcaemia is a low serum albumin with normal ionised calcium concentration.. Conversely, ionised calcium may be low in the face of normal total serum calcium if the serum is alkalotic-for example, as a result of hyperventilation.

-Magnesium depletion should also be considered as a possible contributing factor, particularly in patients with malabsorption, on diuretic therapy or with a history of alcohol excess

-The most common cause of hypoparathyroidism is damage to the parathyroid glands (or their blood supply) during thyroid surgery, although this complication is only permanent in 1% of thyroidectomies. Transient hypocalcaemia develops in 10% of patients 12-36 hours following subtotal thyroidectomy for Graves' disease. Rarely, hypoparathyroidism can occur as a result of infiltration of the glands, e.g. in haemochromatosis and Wilson's disease

- -There are a number of rare congenital or inherited forms of hypoparathyroidism. One form is associated with autoimmune polyendocrine syndrome type 1 and another with DiGeorge syndrome. Autosomal dominant hypoparathyroidism is the mirror image of familial hypocalciuric hypercalcaemia (FHH); an activating mutation in the calcium-sensing receptor results in hypocalcaemia, .PTH concentrations that are 'inappropriately' low and hypercalciuria
- -In pseudohypoparathyroidism there is tissue resistance to the effects of PTH, such that PTH concentrations are markedly elevated. The features include short stature, short 4th metacarpals and metatarsals, rounded face, obesity and subcutaneous calcification.
- -The term 'pseudo-pseudohypoparathyroidism' is used to describe patients with these clinical features in whom serum calcium and PTH .concentrations are normal

Clinical assessment

-Tetany occurs in all syndromes in which ionised calcium concentrations are low. Additional features are specific to different aetiologies

-Low ionised calcium concentrations cause increased excitability of peripheral nerves. In the absence of alkalosis, tetany usually occurs in adults only if total serum calcium is < 2.0 mmol/l (8 mg/dl). Children are more sensitive than .adults

-In children, a characteristic triad of carpopedal spasm, stridor and convulsions occurs,.

-The hands in carpal spasm adopt a characteristic position. The metacarpophalangeal joints are flexed, the interphalangeal joints of the fingers and thumb are extended, and there is opposition of the thumb

-Stridor is caused by spasm of the glottis.

- Adults complain of tingling in the hands and feet and around the mouth. Less often there is painful carpopedal spasm, while stridor and fits are rare

-Latent tetany may be recognised by eliciting

---Trousseau's sign; inflation of a sphygmomanometer cuff on the upper arm to more than the systolic blood pressure is followed by carpal spasm within 3 minutes.

A less specific sign of hypocalcaemia is that described by Chvostek, in which tapping over the branches of the facial nerve as they emerge from the parotid gland produces twitching of the facial muscles.

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-Hypocalcaemia causes papilloedema and prolongation of the ECG QT interval, which may predispose to ventricular arrhythmias.

-Prolonged hypocalcaemia and hyperphosphataemia (as in hypoparathyroidism) may cause calcification of the basal ganglia, grand mal epilepsy, psychosis and cataracts.

-Hypocalcaemia associated with hypophosphataemia, as in vitamin D deficiency, causes rickets in children and osteomalacia in adults

Management

-To control tetany, alkalosis can be reversed acutely if arterial PCO_2 is increased by rebreathing expired air in a paper bag or administering 5% CO_2 in oxygen.

--Injection of 20 ml of a 10% solution of calcium gluconate slowly into a vein will raise the serum calcium concentration immediately. An intramuscular injection of 10 ml may also be given to obtain a more prolonged effect.

-In severe cases of alkalotic tetany, intravenous calcium gluconate often relieves the spasm, while specific treatment of the alkalosis,

Intravenous magnesium is required to correct the hypocalcaemia associated .with hypomagnesaemia

-Persistent hypoparathyroidism and pseudohypo-parathyroidism are treated with oral calcium salts and vitamin D analogues, either 1α-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol). This therapy needs careful monitoring because of the risks of iatrogenic hypercalcaemia, hypercalciuria and nephrocalcinosis