Hypoparathyroidism

Hypoparathyroidism is characterised by hypocalcaemia, hyperphosphataemia and low or inappropriately normal levels of parathyroid hormone (PTH). Pseudohypoparathyroidism is characterised by similar findings but PTH is elevated due to PTH resistance.[1]

PTH is a key calcium-regulating hormone essential for calcium homeostasis, vitamin D-dependent calcium absorption, renal calcium reabsorption and renal phosphate clearance.[1]

PTH is secreted by the four parathyroid glands, located in the neck behind the thyroid gland. It regulates serum calcium and phosphorus levels and also plays a part in bone metabolism. Low levels of PTH cause serum calcium levels to fall and serum phosphate levels to rise.

Calcium and phosphate homeostasis

- Maintenance of normal serum calcium levels involves the regulation of the flux of calcium between the intestinal tract, kidneys and bone.
- Calcium itself, PTH and 1,25-dihydroxyvitamin D3 all play a role in calcium regulation.
- 1,25-dihydroxyvitamin D3 facilitates intestinal calcium absorption, whilst both 1,25-dihydroxyvitamin D3 and PTH stimulate calcium release from bone.
- PTH also stimulates the conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 enabling distal renal tubular calcium reabsorption.
- High concentrations of serum calcium inhibit PTH secretion while low concentrations stimulate it.
- Phosphate reabsorption from the kidney is reduced by PTH. Thus if PTH levels are low, serum phosphate will rise (more will be reabsorbed).

Epidemiology

- This is a rare disorder.
- Found equally in males and females.
- Age of onset depends on the aetiology.

Aetiology

Hypoparathyroidism may be transient, congenital/genetically inherited or acquired. The most common cause of hypoparathyroidism is iatrogenic following anterior neck surgery.[1]

Transient hypoparathyroidism in the neonatal period

Healthy term neonates undergo a reduction in serum calcium levels by 24-48 hours of age. Some neonates, especially high-risk (eg, infants of mothers with diabetes, preterm infants and infants with perinatal asphyxia), may develop hypocalcaemia. Early-onset hypocalcaemia presents within 72 hours and requires treatment with calcium supplementation for at least 72 hours. Late-onset hypocalcaemia usually presents after seven days and requires longer-term therapy.[2]

- Prematurity at birth: very low birth weight infants may not have a normal PTH surge postnatally, thus resulting in hypocalcaemia.
- Infants of mothers with diabetes: hypomagnesaemia due to maternal magnesuria impairs PTH release and action.
- Delay in PTH surge postnatally: this can occur in otherwise healthy neonates.
- Maternal hyperparathyroidism: this results in hypercalcaemia which can cause prolonged PTH suppression in the neonate.

Congenital or genetically inherited hypoparathyroidism

- Defects in parathyroid gland development:
  - DiGeorge’s syndrome: there is abnormal development of the parathyroid glands from the third and fourth pharyngeal pouches. The thymus gland, aortic arch and parts of the lips and ears also develop from these pouches. There is hypoparathyroidism, T-cell immune deficiency, abnormal facies such as cleft palate, and cardiac anomalies.

- Defects in the PTH gene.
- Defects in the calcium-sensing receptor gene:
  - Presents as hypocalcaemia, inappropriately normal levels of PTH and raised phosphate levels.
  - This is not true hypoparathyroidism but its presentation mimics it.
  - Can present from birth to adulthood.
Defects in PTH action (pseudohypoparathyroidism): this occurs when the somatic features of pseudohypoparathyroidism are present in patients with normal serum calcium and phosphate levels. PTH is either normal or raised. The patient may fluctuate between hypocalcaemia and normocalcaemia and may develop cataracts:
- A rare inherited disorder where there is failure of target cells to respond to PTH, i.e., there is PTH resistance.
- PTH levels are not low but are appropriate for the degree of hypocalcaemia.
- There is an association with:
  - Somatic anomalies.
  - Short stature.
  - Round face.
  - Short neck.
  - Shortening of the metacarpals and metatarsals.
  - Hypothyroidism.
  - Diabetes mellitus.
  - Gonadal dysgenesis.
- As part of an autoimmune process:[3]
  - Autoimmune polyglandular syndrome type 1 (APS-1): autosomal recessive inheritance. Features include hypoparathyroidism, adrenal insufficiency, chronic mucocutaneous candidiasis. Also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Presents in childhood.
- Isolated hypoparathyroidism with a possible autoimmune cause can also be inherited.
- Genetic syndromes, including:
  - Hypoparathyroidism, deafness and renal (HDR) dysplasia syndrome.
  - Hypoparathyroidism, retardation and dysmorphism (HRD) syndrome.

Acquired hypoparathyroidism
- Neck surgery (thyroid, parathyroid, laryngeal or oesophageal surgery) is the most common cause and includes:
  - Accidental damage to, or accidental removal of, the parathyroid glands. Most likely during thyroid surgery. May be transient or permanent. Surgeon-dependent.[4, 5]
  - Removal of parathyroid glands because of potential malignancy.
  - After surgery for hyperparathyroidism. Transient hypoparathyroidism may occur whilst the body returns to a normal response to PTH.
- Radiation or drugs:
  - Neck or chest irradiation during radiotherapy treatment.
  - Radioactive iodine treatment for hyperthyroidism: a rare side-effect.
  - Chemotherapeutic/cytotoxic agents.
  - Alcohol.
- Infiltration of the parathyroid glands:
  - Destruction of the parathyroid glands due to iron deposition can occur in haemochromatosis or multiple blood transfusions.
  - Destruction of the parathyroid glands due to copper deposition can occur in Wilson's disease.
  - Infiltration of the parathyroid glands by malignant metastases.
- Magnesium deficiency, which can occur in:
  - Chronic alcoholism.
  - Burns.
  - Hereditary renal or intestinal hypomagnesaemia.[6]
- Magnesium excess - e.g., when magnesium is used for the treatment of preterm labour or pre-eclampsia.[6]
- Autoimmune process: sporadic forms of APS-1 can occur as described above.
- Isolated idiopathic hypoparathyroidism:
  - PTH deficiency is present but no other associated endocrine or developmental disorders.
  - Usually sporadic but can be familial.
  - May possibly be a form of autoimmune hypoparathyroidism.

Pseudohypoparathyroidism[7]
Pseudohypoparathyroidism includes a heterogeneous group of rare metabolic disorders that include characteristic morphological features and end-organ resistance to the action of PTH. Plasma concentrations of PTH are elevated and reflect the failure of target tissues to respond appropriately to the biological actions of PTH.

Pseudopseudohypoparathyroidism
This is very rare and occurs when there is no endocrine abnormality but the morphological features are otherwise the same as for pseudohypoparathyroidism.[6, 9]

Presentation
is essentially with the symptoms of hypocalcaemia. Hypocalcaemia may be an asymptomatic laboratory finding or a life-threatening metabolic disturbance. Symptoms include:

- Muscle pains.
- Bone pain: bone turnover is abnormally low and bone mineral density is typically increased.
- Abdominal pain.
- Paraesthesiae (tingling, vibrating, burning and numbness) of the face, fingers and toes.
- Facial twitching.
- Carpopedal spasm.
- Stridor.
- Convulsions (usually grand mal).
- Syncope.
- Emotional lability, anxiety and depression, confusion.
- Memory impairment.
- Lethargy.
- Headaches.
- Brittle nails.
- Dry hair and skin.
- Painful menstruation.

Important points to elicit in the history include:

- History of previous neck surgery.
- Family history of any hypoparathyroid disorders.
Clinical signs

- Chvostek's sign: detects latent tetany:
  - Tapping of the fifth facial nerve in front of the ear with the patient's mouth slightly open causes contraction of the facial muscles.
  - Not specific, as about 25% of the normal population have a positive response.

- Trousseau's sign: occlude the arterial circulation of the forearm using a blood pressure cuff inflated to the systolic blood pressure for three minutes. Carpopedal spasm is induced.
  - Raised intracranial pressure with papilloedema.
  - Cataracts.
  - Dental abnormalities and enamel dysplasia.
  - Brittle nails with transverse grooves.
  - Dry, rough skin.
  - Hyperreflexia.

Other symptoms and signs depend on the aetiology:

- DiGeorge's syndrome:
  - Recurrent infections due to T-cell immunodeficiency.
  - Congenital heart disease and its related symptoms, heart murmur.
  - Speech delay.
  - Abnormal facies: cleft palate, micrognathia, ear abnormalities.

- Familial autoimmune polyglandular syndrome type I (APS-I):
  - Chronic mucocutaneous candidiasis.
  - Adrenal failure.
  - Vitiligo.
  - Dental enamel hypoplasia.

- Genetic syndromes:
  - Sensorineural deafness.
  - Renal dysplasia.
  - General learning disability.

Differential diagnosis

Hypocalcaemia and hyperphosphatataemia can also be caused by:[11]

- Magnesium deficiency.
- Vitamin D deficiency.
- Chronic kidney disease: may develop secondary hyperparathyroidism.[13]
Investigations

- Blood tests (to exclude other causes of hypocalcaemia):
  - Calcium, phosphate, PTH and alkaline phosphatase:

  Typical blood test results in hypoparathyroidism:
  - Low serum calcium.
  - High serum phosphate.
  - Low PTH.
  - Normal alkaline phosphatase.

  Typical blood test results in pseudohypoparathyroidism:
  - Low serum calcium.
  - High or normal PTH.

  - Serum magnesium: may be low.
  - U&Es: to exclude chronic kidney disease.
  - 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3: to exclude vitamin D deficiency as a cause of hypocalcaemia. 25-hydroxyvitamin D3 is normal in hypoparathyroidism and pseudohypoparathyroidism but 1,25-dihydroxyvitamin D3 is low because PTH is not available for its activation.

  - Additional blood tests:
    - If an autoimmune process is suspected, look for coinciding thyroid and adrenal insufficiency:
      - Thyroid-stimulating hormone (TSH), thyroxine and thyroid autoantibodies.
      - Adrenocorticotropic hormone (ACTH) and adrenal antibodies.

  - Urine tests: 24-hour urinary calcium is usually low.
  - Other possible investigations:
    - ECG: prolonged QT interval which may progress to ventricular fibrillation or heart block.
    - Echocardiogram: cardiac abnormalities (in DiGeorge's syndrome).
    - Renal ultrasound: looking for renal calculi.
    - Hand radiography: looking for shortened metacarpals.
    - Brain MRI scan: basal ganglia calcification (sign of a long-standing hypocalcaemic state).
    - Genetic studies: as appropriate.

Treatment

Acute treatment

- If severe hypocalcaemia symptoms are present, such as tetany, urgent IV calcium should be given.[14]

Dietary advice

- A diet rich in dairy products containing calcium and vitamin D is recommended.

Calcium and vitamin D3

- The basis of treatment is with calcium and vitamin D.[15]
- The doses are tailored to the individual's needs and regular monitoring is needed.
- In some people, once adequate doses of vitamin D are achieved, they can absorb all the calcium that they need through the diet. However, in others, calcium levels remain permanently unstable and maintenance doses of calcium and vitamin D will need to be regularly monitored and adjusted.
- Treatment is lifelong.
- There is no restriction on activities but patients should wear a bracelet to identify themselves as suffering from hypoparathyroidism.

PTH

- As yet, PTH is not commercially available to treat hypoparathyroidism.[16]
- However, recombinant PTH is used for the treatment of postmenopausal osteoporosis.[17]
- PTH replacement improves serum calcium and lowers serum phosphate. It has been shown to lower urinary calcium loss.[1]
- Careful monitoring of vitamin D, phosphorous, and calcium is necessary during acute and long-term therapy.[1]

Parathyroid autotransplantation and allotransplantation

- If a patient has a thyroidectomy, one of the parathyroids can be 'autotransplanted' into either the neck or the forearm to give a continuing supply of PTH.[18]
- Allotransplantation of cultivated parathyroid tissue is also a possibility.[19]
Potential treatment problems

- Pregnancy, diuretics, antacids, anticonvulsants, intercurrent illness, ammonium chloride and acetazolamide may alter the requirements for vitamin D.
- Close monitoring of calcium levels is needed.
- There has been one case report of hypoparathyroidism refractory to vitamin D therapy, treated with multipulse teriparatide. [65]

Complications

Mostly due to hypocalcaemia:

- Laryngospasm can cause stridor and airway obstruction.
- Neuromuscular irritability can lead to muscle cramps, tetany and seizures.
- Heart: QT interval changes can cause syncope, arrhythmias and death.
- Calcium can be deposited in the kidneys, causing calculi.
- Stunted growth, malformed teeth and mental impairment can develop if untreated in childhood.
- Over-treatment with vitamin D can cause hypercalcaemia and renal impairment.

Prognosis

- The regular monitoring required to ensure appropriate calcium levels means that the prognosis is challenging for many people. This may improve if synthetic PTH becomes widely available.
- Regular review and blood monitoring programmes within the GP setting are likely to be beneficial.

Prevention

Close monitoring of patients undergoing thyroid or neck surgery, radiotherapy to the neck or chest and chemotherapy treatment for symptoms and signs of hypocalcaemia.

Further reading & references

6. Understanding the Causes of Hypoparathyroidism; Hypoparathyroidism UK. July 2017
13. British National Formulary
17. British National Formulary

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