Hypoparathyroidism

This department covers selected points from the 2010 Canadian Endocrine Update: A CME Day from the Division of Endocrinology and Metabolism at McMaster University and the University of Western Ontario.
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Hypoparathyroidism is a rare hormone deficiency resulting in hypocalcemia, as parathyroid hormone (PTH) secretion is inadequate.[1,2]

Etiology and Associated Conditions

The chief cells of the parathyroid glands normally secrete PTH in response to low serum calcium levels. The function of PTH is to maintain plasma calcium levels in a tightly defined normal range by enhancing renal calcium reabsorption, increasing osteoclastic bone resorption, and increasing vitamin D hydroxylation and thus increasing calcium absorption from the bowel.[1] Hypoparathyroidism is the only remaining hormonal insufficiency condition that is currently not being treated with direct replacement of the deficient hormone.[3]

The typical laboratory characteristics include hypocalcemia, hyperphosphatemia, and low PTH levels. Hypoparathyroidism may be secondary to parathyroid surgery or be autoimmune, familial, or idiopathic in origin. Hypoparathyroidism is most commonly the result of irreversible damage to, or removal of the parathyroid glands during thyroidectomy, parathyroidectomy, or radical neck surgery.[4] This complication is seen in 0.5 to 6% of total thyroidectomies, and is directly related to the surgeon's experience, extent of resection, and underlying conditions.[1,5-11]

Autoimmune hypoparathyroidism is seen in the setting of polyglandular endocrinopathies, particularly autoimmune polyendocrine syndrome type I (APS-1). Patients with PTH-deficiency and hypocalcemia of unknown origin are simply diagnosed as having idiopathic hypoparathyroidism. Mutations in the transcription factor autoimmune regulator (AIRE) protein may be involved in both conditions.[12]

Patricia's Case

Patricia, a 45-year-old accountant, is in your office to review her blood work. Her total calcium is 1.72 mmol/L and parathyroid hormone (PTH) is 1.4 pmol/L. Her past medical history includes thyroid cancer, for which she had a total thyroidectomy two months ago. She is taking a PPI for GERD, and 400 IU of vitamin D3 supplementation q.d. She complains of muscle cramping and numbness of her lower lip.

What further investigations need to be ordered? If hypoparathyroidism is confirmed, what is her long-term management?

Read on for the answers to Patricia's case.

Genetic causes include DiGeorge syndrome and the closely related velocardiofacial syndrome, autosomal dominant activating mutations of the parathyroid and renal calcium sensing receptor (CaSR), and familial mutations in transcription factors (*e.g.*, GCMB, GCM2, GATA3).[1,2,12-18] Other uncommon causes include heavy metal infiltration of the parathyroid glands with iron accumulation from hemochromatosis or transfusions, or copper deposition in Wilson's disease.[1] Metastatic infiltration of the parathyroid glands can also result in hypoparathyroidism[1], as can magnesium deficiency or excess.[1,19]

Hypothyroidism is most commonly the result of irreversible damage to, or removal of the parathyroid glands.

Diagnosis of hypoparathyroidism

Clinical features

Patients with hypoparathyroidism often present with:

- Hypocalcemia (symptomatic or asymptomatic)
- Hypercalciuria
- Hyperphosphatemia

Hypocalcemia can be potentially life-threatening, and is most commonly characterized by paresthesias, muscle spasms, tetany, seizures, or circumoral or acral numbness. Altered mental status, refractory congestive heart failure, or stridor can also occur.[1,19] Muscle weakness is related to the degree of hypocalcemia.[20] In chronic hypocalcemia, patients may be asymptomatic, despite having significantly low serum calcium levels.[1]

It is essential to inquire about family history, past head or neck surgeries, and known autoimmune conditions (signs may include oral candidiasis or adrenal insufficiency).[13] Upon physical examination, look for any evidence of neck scarring indicative of previous surgery. Chvostek's sign (low specificity and sensitivity, with 25% of normal individuals having a positive sign, and 29% of hypocalcemic patients have negative sign) is seen as twitching of the upper lip when tapping on the cheek 2 cm anterior to the earlobe, below the zygomatic process overlying the facial nerve.[12] Trousseau's sign (more reliable, present in 94% of hypocalcemic individuals and only 1 to 4% of healthy people) can be observed if a blood pressure cuff is applied over systolic pressure for three minutes, which will produce a carpal spasm in hypocalcemia patients.[1,12,21] Signs of oral candidiasis, vitiligo, bronze skin, stigma of liver disease, growth or mental retardation, congenital anomalies, or hearing loss can all suggest the presence of an underlying genetic disease.[1] Renal manifestations include nephrolithiasis, nephrocalcinosis, and renal dysfunction.

Patricia's Case, Con't

Serum total calcium should be corrected for serum albumin: Corrected total calcium (mmol/L) = Measured calcium (mmol/L) + (40 - serum albumin [g/L]) * 0.02. Serum ionized calcium, PTH, magnesium, phosphate, creatinine, albumin, and 25(OH) vitamin D should be ordered. Other investigations include $1,25(OH)_2D_3$, electrolytes, 24 hour urine calcium, magnesium and creatinine, renal U/S to assess for nephrocalcinosis and renal stones, and genetic analysis.

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Laboratory findings

Laboratory investigations should include total and ionized calcium, serum albumin, phosphate, magnesium, creatinine, PTH, and $25(OH)D_3$.[1] Ionized serum calcium is the preferred form of serum calcium to measure.[2] 24 hour urinary calcium, magnesium, and creatinine levels should also be measured to evaluate renal function and losses.[1] The measurement of $25(OH)D_3$ is necessary to rule out vitamin D deficiency; furthermore, measurement of $1,25(OH)_2$ vitamin D is generally not required in initial investigations.[1] A typical laboratory profile of hypoparathyroid patients will reveal hypocalcemia, low PTH levels, hyperphosphatemia (phosphaturic effect of PTH is lost), hypercalciuria, and low $1,25(OH)_2D_3$.[1] PTH levels can be inappropriately normal in hypomagnesemia or with activating gain-of-function CaSR mutations.[22]

Hypocalcemia occurring after parathyroidectomy for the treatment of primary hyperparathyroidism can be due either to hungry bone syndrome or hypoparathyroidism.[12] Serum phosphorus is usually low in hungry bone syndrome, which is associated with vitamin D insufficiency and is high in hypoparathyroidism.[12] In patients with CaSR activating mutations, the calcium to creatinine ratio has been reported to be significantly higher than in those with other causes of hypoparathyroidism.[23]

Specialized testing can include gene sequencing for the GATA3 or AIRE protein, microarray or hybridization to diagnose DiGeorge syndrome or velocardiofacial syndrome, and hormone tests to detect APS-type 1.[1,16,17] DNA analysis can be completed to search for mutations in the following genes: CaSR, glial cells missing B (a specific transcription factor controlling parathyroid gland development), PTH, and GS-α subunit protein (GNAS gene).[1] Availability and access to these specialized tests is dependent on the policies of the laboratory centre receiving the requisitions.

A typical laboratory profile of hypoparathyroid patients will reveal hypocalcemia, low PTH levels, hyperphosphatemia, hypercalciuria, and low $1,25(OH)_2D_3$.

Management of hypoparathyroidism

There are currently no formal guidelines addressing the management of hypoparathyroidism, and approach is based on clinical judgment tailored to the needs of the patient.[1] Close laboratory monitoring is required, particularly of renal function and serum

calcium. The primary goals of management include: control of symptoms, maintaining serum calcium in the low to normal range, maintaining serum phosphorus within normal limits, maintaining 24 hour urine calcium under 7.5 mmol/day (300 mg/day), and maintaining a calcium-phosphate product under 55 mg^2/dL^2 (4.4 $mmol^2/L^2$) as many patients develop nephrolithiasis, nephrocalcinosis, and soft-tissue calcifications.[1,12,24]

Acute management of hypocalcemia consists primarily of IV calcium if patients have severe symptoms or serum calcium under 1.9 mmol/L (7.5 mg/dL).[1,25,26]

Current long-term treatment options for hypoparathyroidism include the use of calcium, vitamin D metabolites and analogues, thiazide diuretics, phosphate binders and a low-salt and low-phosphate diet.[1] The most commonly recommended calcium supplements are calcium carbonate (requires acidic gastric pH for optimal absorption) and calcium citrate (particularly of value in those with achlorohydria).[1,4,27] Most regimens involve dosing over 1 g/day of elemental calcium, typically in several divided doses.[1] Elemental calcium can be administered as 400 to 800 mg doses every six hours, and 1 to 2 g TID may be required.[1] $1,25(OH)_2D_3$ maintains serum calcium by optimizing intestinal calcium absorption and promoting bone remodeling.[4,28] Calcitriol is the most active metabolite, and has a rapid onset and offset of action.[1,13] The usual starting dose is 0.5 µg/day, with doses adjusted every four to seven days as needed.[4,19] Alphacalcidiol, dihydrotachysterol, vitamin D3 (cholecalciferol), and vitamin D2 (ergocalciferol) are also considered for use; however, they are limited by their relatively reduced efficacy and long half-lives.[4] Hydrochlorothiazide and other thiazide diuretics are effective in reducing urinary calcium excretion.[1,13] Phosphate levels can be lowered by reducing phosphate intake and using phosphate binders to avoid metastatic calcification.[1]

Complications of treatments include hypercalcemia, hypercalciuria, and vitamin D intoxication. Patients should be monitored every one to two weeks during initial regimen adjustments, and should be seen in follow-up once every three to six months after a stabilized regimen has been established.[1,19] Patients with activating mutations of the CaSR gene are at particularly high risk of renal complications and hypercalciuria; therefore, a more cautious use of vitamin D metabolites is advised for this population.[2,14,23,29,30] Dx

Patricia's Case, Con't

Recommended oral calcium supplements are calcium carbonate and calcium citrate (latter preferred when taking PPIs), starting with 500 to 1000 mg TID of elemental calcium. In addition to vitamin D supplements, Patricia should receive calcitriol or alfacalcidol, starting with a dose of 0.5-1 µg/day. All doses should be adjusted as needed.

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