HYPOCALCEMIA

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CLINICAL RECOGNITION

Hypocalcemia can occur acutely over minutes to hours or chronically over weeks to months. Correspondingly, the signs and symptoms of hypocalcemia can develop acutely or chronically and can be life-threatening. The clinical manifestations of hypocalcemia are due to the increased neuromuscular tingling in the extremities and around the mouth. Chvostek's and Trousseau's signs can be elicited. When severe, tetany, convulsions, laryngospasm and bronchospasm can occur. Hypocalcemic symptoms are a result of both the absolute level of serum calcium and the rate of change in serum calcium concentration. Major signs and symptoms of hypocalcemia are summarized in Table 1.

Table 1. Signs/Symptoms of Hypocalcemia
I. Neuromuscular
. Paresthesias - perioral and extremities
. Muscle spasms
. Laryngeal stridor, bronchospasm
. Seizures
. Cardiac arrhythmias
. Coma
. Chvostek's sign
. Trousseau's sign (main d'accoucheur)
. Tetany - Clinical or latent
. Pseudotumor cerebri
. Papilledema
II. Cardiovascular
. Arrhythmias
. Hypotension
. Congestive heart failure
III. Other
. Cataracts - subcapular, punctate
. Extra-skeletal calcifications - Basal ganglia, Ligamentous and soft tissue

. Dental enamel hypoplasia . Alopecia . Xeroderma

DIAGNOSIS AND DIFFERENTIAL

The major causes of hypocalcemia are summarized in Table 2.

Table 2. Major Causes of Hypocalcemia
Renal failure
Hypoparathyroidism (see Table 3)
Magnesium deficiency
Pancreatitis
Osteoblastic metastases
Hyperphosphatemia
Pseudohypocalcemia (e.g., hypoalbuminemia, gadolinium-contrast agents)
Massive transfusion of citrated blood products
Osteomalacia
Malabsorption
Vitamin D deficiency
Vitamin D receptor defect(s)
Calcium-sensing receptor (CaSR) constitutive activating mutations
Drugs (e.g., imatinib, bisphosphonates, denosumab, calcitonin)

Renal Failure

Hypocalcemia in chronic renal failure is due to two primary causes - increased serum phosphorus and decreased renal production of 1,25 (OH)2 vitamin D. The former causes hypocalcemia by complexing with serum calcium and depositing it into bone and other tissues. The latter causes hypocalcemia by decreasing the GI absorption of calcium.

Hypoparathyroidism

There are several causes of hypoparathyroidism, as summarized in Table 3. Neck surgery that removes or destroys the parathyroid glands is the most common cause of hypoparathyroidism. These operations include: (1) thyroidectomy due to thyroid cancer or benign goiter, with inadvertent removal or destruction of parathyroid tissue; (2) parathyroidectomy, especially for multigland hyperplasia; and (3) laryngectomy. Post-surgical hypoparathyroidism can occur within hours after surgery or gradually over time when glands injured at surgery ultimately become non-functioning.

Idiopathic hypoparathyroidism can occur in isolation or in association with other endocrine or autoimmune disorders (Table 4), typically with adrenal insufficiency. The parathyroid glands can be absent, remnant, or compromised by an immune destruction. Anti-cytokine antibodies (e.g., against alpha interferons) or antibodies directed against parathyroid cell antigens (e.g., NALP5) may be present.

Pseudohypoparathyroidism (PHP) is a genetic disorder characterized by target-organ unresponsiveness to PTH. PHP mimics the hormone-deficient forms of hypoparathyroidism, with hypocalcemia and hyperphosphatemia, but PTH levels are elevated rather than low or absent.

Hypoparathyroidism can occur in an autoimmune setting (Table 4) associated with autoantibodies. The most commonly associated disorders are Addison disease and mucocutaneous candidiasis. Two of the 3 disorders in the triad are necessary for the diagnosis of APS1. These patients can be affected by other endocrinopathies or immune-mediated disorders (e.g., thyroid disease, diabetes mellitus, pernicious anemia, and ovarian failure).

TABLE 3. Causes of Hypoparathyroidism
Postoperative - acute and chronic Parathyroidectomy Thyroidectomy Cancer surgery – laryngeal, thyroid
Idiopathic Isolated Associated with autoimmune polyendocrine syndrome
Functional Magnesium deficiency (or excess) Newborn of mother with hyperparathyroidism
Pseudohypoparathyroidism (Types 1a, 1b, 2)
Genetic disease DiGeorge Syndrome - aplasia/dysgenesis of the parathyroids and thymus along with other features Activating mutation of the calcium-sensing receptor (CaSR) or of the G protein subunit G alpha 11 PTH gene mutation GATA3 deficiency GCMB deficiency Mitochondrial DNA mutations
Infiltration of the glands Iron deposits (Hemochromatosis, transfusions) Copper deposits (Wilson's Disease)
Radiation to neck
Metastases to the parathyroid glands from non-parathyroid tumors
Magnesium deficiency
Drugs (e.g., calcimimetics cinacalcet and etelcalcitide)

TABLE 4. Autoimmune Polyendocrine Syndrome Type 1 (APS1) Associated with Hypoparathyroidism
Mucocutaneous candidiasis Addison disease Hypothyroidism Grave's disease Hypogonadism

Vitiligo
Alopecia
Malabsorption (steatorrhea)
Chronic active hepatitis
Pernicious anemia
Diabetes mellitus
Keratoconjunctivitis

Other Causes of Hypocalcemia

Magnesium deficiency causes hypocalcemia by interfering with the end-organ actions of PTH and/or by inhibiting its secretion. Pancreatitis causes hypocalcemia through sequestration of calcium by saponification with fatty acids. Osteoblastic metastases similarly take up blood calcium. Excessive transfusion of citrated blood products may transiently lower ionized calcium and cause symptoms until citrate is cleared by the liver. In hyperphosphatemia, high levels of blood phosphorus complexes with calcium, and the product can precipitate into organs and soft tissues. Causes include renal failure, administration of phosphate, rhabdomyolysis, tumor lysis, and some cases of tumoral calcinosis. Vitamin D deficiency (or resistance syndromes) contributes to the hypocalcemia of osteomalacia and malabsorption. Iatrogenic causes include cancer chemotherapy, notably certain tyrosine kinase inhibitors. Other drugs reported to cause hypocalcemia include inhibitors of bone resorption, loop diuretics, and agents that accelerate vitamin D metabolism, like anticonvulsants. All inhibitors of bone resorption used to treat hypercalcemia (e.g., calcitonin, intravenous bisphosphonates, the receptor activator of nuclear factor kappa B ligand or RANK-L inhibitor denosumab) and the calcimimetics cinacalcet or etelcalcitide used to treat hyperparathyroidism can cause hypocalcemia.

DIAGNOSTIC TESTING

The first step in assessing hypocalcemia is to confirm the results and rule out artifactually low calcium due to hypoalbuminemia. In hypoalbuminemic patients, ionized calcium can be measured, or total serum calcium can be corrected using the following formula: corrected Ca=measured Ca + (0.8) X (4- measured albumin). In critically ill patients with acid-base disturbances, measurement of ionized calcium is preferable due to altered calcium-albumin binding that can occur. Measuring serum phosphorus, PTH, creatinine, and 25 hydroxyvitamin D can usually identify the cause of the hypocalcemia. Interpreting PTH levels must be done in the context of serum calcium concentration. PTH can be low in hypoparathyroidism and hypomagnesemia and high when there is secondary (compensatory) hyperparathyroidism or pseudohypoparathyroidism. The PTH assay used should be an intact assay with reliable performance at the low end of the normal range. Patients with hypoparathyroidism may have a frankly low intact PTH or a low normal PTH that is inappropriate in the presence of hypocalcemia. Additional testing is done according to the clinical presentation and can include magnesium (hypomagnesemia), pancreatic enzymes (lipase), biochemical markers of bone turnover (osteoblastic metastases), ACTH/cortisol, and TSH (polyendocrine failure), and 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D (deficiency states). Imaging can be useful for bone disease (osteomalacia, osteoblastic metastases).

TREATMENT

Acute Hypocalcemia

Hypocalcemia can be an endocrine emergency requiring rapid intervention. Patients with either

severe hypocalcemia, usually <7.5 mg/dl, or with neurological manifestations or stridor (laryngo/bronchospasm) should receive intravenous calcium. Calcium gluconate (90 mg calcium per 10 mL) should be given as intravenous slow pushes, generally one vial over 10 minutes, repeated once with electrocardiographic monitoring. A chronic intravenous drip is then started if the patient is still symptomatic and oral treatment cannot act rapidly enough. The infusion rate should be guided by signs, symptoms, and calcium measurements checked every 1-2 hours, preferably ionized calcium levels. Magnesium deficiency should also be treated when present, since it can attenuate the effect of the treatment by calcium and vitamin D (see below). Oral calcium (e.g., 1-2 grams of elemental calcium) and a rapidly acting preparation of vitamin D (e.g., 0.5-1.0 micrograms of calcitriol in divided doses) should be started as soon as practical. This is often limited by neck surgery. If necessary, intravenous calcium can be given for as long as necessary until oral therapy has taken effect. Patients taking cardiac drugs, especially digoxin, are predisposed to cardiotoxicity by the infusion of calcium, so an EKG should be used for cardiac monitoring. Treatment must be assessed with frequent serum ionized calcium levels. Several preparations of calcium for oral use are available. The most commonly used are calcium carbonate and calcium citrate (Table 5). Recombinant human PTH(1-84) has been recently approved for the treatment of chronic hypoparathyroidism in adults and can reduce the amount of calcium and activated vitamin D supplements that a patient is required to take to control serum calcium levels in this disorder. However, in the United States this drug was removed from formularies because of rubber particulates discovered in the solution. Hopefully, this problem will be resolved soon. In the meantime, some clinicians are using other PTH preparations.

TABLE 5. CALCIUM PREPARATIONS

Grams to provide 1 gm of elemental calcium	
Carbonate	2.5
Chloride	3.7
Acetate	4.0
Citrate	5.0
Glycerolphosphate	5.7
Levulinate	7.7
Lactate	7.7
Orthophosphate	9.0
Gluconate	11.1
Glubionate	15.2

Hypomagnesemia should always be considered as a potential contributory cause of hypocalcemia, especially in post-operative and hospitalized patients. Low serum magnesium may reveal this, but the serum magnesium may be normal or low normal, since serum magnesium does not accurately reflect the stores of this primarily intracellular ion. Therefore, a therapeutic trial of magnesium, usually parenteral, may be needed to assess for magnesium deficiency. Oral magnesium is used for mild, chronic magnesium deficiency (e.g., daily dose of 200-300 mg). Many preparations are available including magnesium oxide, magnesium carbonate or magnesium sulfate. Parenteral magnesium (10% or 50% solutions of magnesium sulfate) is used for severe hypomagnesemia. A common regimen is 2-4 mls IV of a 50% solution given over 10-15 minutes followed by similar amounts given daily. Several days of treatment are usually required to replete magnesium stores.

Chronic Hypocalcemia

The objective of chronic therapy for hypocalcemia is to keep the patient free of symptoms and to maintain serum calcium at approximately 8.0-9.0 mg/dL. With lower serum calcium levels, the patient may continue to experience symptoms over time. With serum calcium concentrations in the upper normal range, there may be significant hypercalciuria, especially when the hypocalciuric effect of PTH has been lost. This can predispose to nephrolithiasis, nephrocalcinosis, and renal damage. When the calcium x phosphorus product rises to near 55 mg^2/dL^2 or greater, as it can in patients with hypoparathyroidism who also have a chronically elevated serum phosphorus level (due to the loss of PTH actions in the kidney), ectopic calcifications in other soft tissues like the brain (especially the basal ganglia), blood vessels, and eyes can occur.

Calcium and vitamin D are used to treat most causes of chronic hypocalcemia, such as renal failure and hypoparathyroidism. Vitamin D is used to establish a baseline calcium level and calcium is added (or subtracted) for acute changes in calcium. Calcitriol is the preferred preparation of vitamin D because it is rapidly active and has a short half-life (i.e., rapidly reversible) in contrast to the other forms of vitamin D (Table 6). In patients with renal failure, treatment is directed at maintaining normal levels of calcium, phosphorus, and the calcium x phosphorus product and the intact PTH within an acceptable range for the chronic kidney disease. 1,25 dihydroxy-vitamin D or calcitriol or one of its analogs can be given orally or parenterally. Vitamin D2 or D3 may be used for nutritional deficiency. Recombinant human PTH(1-84) has been approved for the treatment of chronic hypoparathyroidism in adults and can reduce the amount of calcium and activated vitamin D supplements that a patient is required to take to control serum calcium levels in this disorder. However, in the United States this drug was removed from formularies because of rubber particulates discovered in the solution. Hopefully, this problem will be resolved soon. In the meantime, some clinicians are using other PTH preparations.

Table 6. Vitamin D Preparations for Hypocalcemia Treatment

Name	Daily dose	Time until normocalcemia	Duration of action
Vitamin D_2 (Ergocalciferol)	400 units	4-8 weeks	2-6 months
Vitamin D_3 (Cholecalciferol)	Same as D_2	Same as D_2	Same as D_2
1,25$(OH_2)D_3$ (Calcitriol)	0.25-0.5µg	2-5 days	1-2 days

FOLLOW-UP

The hypocalcemic patient should be periodically followed clinically (for signs and symptoms of recurrence**)** and biochemically (with serum calcium measurements, and less frequently with urinary calcium measurements**).** Other tests, such as magnesium and PTH, can be conducted as clinically indicated. Optimal therapy is best maintained by manipulating few variables, so patients on both vitamin D and calcium should hold vitamin D doses constant and change the oral intake of calcium when signs, symptoms, or measurements of calcium so dictate. Most patients can be treated with a reasonable degree of success, but some patients have frequent swings in symptoms, even though serum calcium levels are not abnormal.

GUIDELINE REFERENCES

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