26-Hypocalcemia Management.

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CLINICAL RECOGNITION

Hypocalcemia can occur acutely over minutes to hours, as in post-parathyroidectomy hypocalcemia, or chronically over weeks to months, as during the development of renal failure. Correspondingly, the signs and symptoms of hypocalcaemia can develop acutely or chronically and can be life-threatening. These clinical manifestations can signal the presence of hypocalcaemia, along with the measurement of serum calcium. The clinical manifestations of hypocalcemia are due to the increased neuromuscular excitability that can accompany a low serum calcium level. Patients complain of paresthesias and tingling in the extremities and around the mouth. Chvostek and Trousseau signs can be elicited. Tetany, convulsions, laryngospasm and bronchospasm are the frankest manifestations of the increased neuromuscular irritability. Hypocalcemic symptoms relate to the absolute level of serum calcium and to the rate of change in the serum calcium concentration. Major signs and symptoms of hypocalcemia are summarized in **Table 1**.

Table 1-Signs and Symptoms of Hypocalcemia

I. Neuromuscular

. Paresthesias - mouth and extremities

. Muscle spasms

Laryngeal stridor, bronchospasm

. Seizures

. Cardiac arrhythmias

Coma

. Chvostek sign

. Trousseau sign - main d'accoucheur

. Tetany - Clinical or latent

. Pseudotumor cerebri

. Papilledema

II Cardiovascular

. Arrhythmias

. Hypotension

. Congestive heart failure

III.Other

. Cataracts - subcapular, punctate

. Extraskeletal calcifications

. Basal ganglia

Ligamentous and soft tissue

. Dental enamel hypoplasia

. Alopecia

. Xeroderma

IV.Surgical neck scar (if due to thyroidectomy)

PATHOPHYSIOLOGY

DIAGNOSIS and DIFFERENTIAL

The major causes of hypocalcemia are summarized in **Table 2.**

Table 2

Renal failure
Hypoparathyroidism (seeTable 3)
Magnesium deficiency
Pancreatitis
Osteoblastic metastases
Hyperphosphatemia
Hypoproteinemia (hypoalbuminemia)
Massive transfusion of citrated blood products
Osteomalacia
Malabsorption
Vitamin D deficiency
Vitamin D receptor defect(s)
Calcium-sensing receptor (CaSR) constitutive activating mutations
Tyrosine kinase inhibitors, e.g., imatinib
Drugs

Renal failure: The pathogenesis of 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 summarized in **Table 3.** Neck surgery (thyroidectomy, parathyroidectomy, laryngectomy) that removes or destroys the parathyroid glands is among the most common cause of hypoparathyroidism. The most common neck surgeries causing hypoparathyroidism are thyroid cancer surgery leading to thyroidectomy, with inadvertent removal or destruction of parathyroid tissue, and parathyroidectomy, especially for multigland hyperplasia. Post-surgical hypoparathyroidism can occur within hours after surgery or gradually over time when glands injured at surgery ultimately become non-functioning.

Idiopathic hypoparathyroidism: Idiopathic hypoparathyroidism can occur by in isolation or in association with other endocrine or autoimmune disorders **(Table 3),** typically with adrenal insufficiency . The parathyroid glands can be absent, remnant, or compromised by an immune destruction. Circulating anti-parathyroid cell antibodies may be present, but their pathogenetic role is not established. Anti-cytokine antibodies (e.g., against alpha interferons) may also be present.

Pseudohypoparathyroidism: 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 and Polyglandular Failure: Hypoparathyroidism can occur in an autoimmune setting **(Table 3)** 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).

Magnesium Deficiency. Magnesium deficiency causes hypocalcemia by interfering with the end-organ actions of PTH and/or by inhibiting its secretion. **Pancreatitis.** 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 are 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**. I**atrogenic 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 interfere with vitamin D metabolism, like anticonvulsants. All inhibitors of bone resorption used to treat hypercalcemia (e.g., calcitonin, gallium, intravenous bisphosphonates, the receptor activator of nuclear factor kappa B ligand or RANK-L inhibitor denosumab) can cause hypocalcemia.

TABLE 3. Causes of Hypoparathyroidsm

Postoperative - acute and chronic
Parathyroidectomy
Thyroidectomy
Cancer surgery – laryngeal, thyroid
Idiopathic
Isolated
Associated with polyglandular failure (autoimmune polyglandular failure type 1 or APS1) (see Table 3A)
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
Activating mutation of the calcium-sensing receptor (CaSR)
PTH gene mutation
GATA3 deficiency
GCMB deficiency
Mitochondrial DNA mutations
Infiltrative
Iron deposits - Hemochematosis as in thalassemia
Copper deposits - Wilson’s Disease
Aluminum deposits - renal disease, aluminum exposure
Radiation to neck
Magnesium deficiency
Drugs (e.g., calcimimetic cinacalcet)

TABLE 3A. Autoimmune polyglandular failure type 1 (APS1) associated with hypoparathyroidism

Mucocutaneous candidiasis

Addison disease

Hypothyroidism

Graves disease

Hypogonadism

Vitiligo

Alopecia

Malabsorption (steatorrhea)

Chronic active hepatitis

Pernicious anemia

Diabetes mellitus

Mucocutaneous candidiasis

Graves' disease

12. Keratoconjunctivitis

DIAGNOSTIC TESTING

In addition to confirming the hypocalcemia, measuring the serum phosphorus, PTH, creatinine, and 25 hydroxyvitamin D can usually identify the cause of the hypocalcemia. Interpreting PTH measurements must be done in the light of serum calcium concentration, and it can be low in hypoparathyroidism and hypomagnesemia and high when there is secondary (compensatory) hyperparathroidism 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. Artifactual causes of hypocalcemia should be ruled out by documenting a low serum albumin (liver disease, nephrotic syndrome) and or a normal ionized calcium level. Total serum calcium can be corrected for the presence of hypoalbuminemia by one of several formulas, where, in general, one gram reduction in the serum albumin level depresses the serum calcium by 0.8 mg/dL. 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 (polyglandular 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 mgs/dl, or with neurological manifestations or stridor (laryngo/bronchospasm) should receive intravenous calcium as calcium gluconate (90 mg calcium per 10 mL) 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 every 1-2 hours, preferably of 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 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 4)**. Recombinant PTH for treatment of chronic hypoparathyroidism is under evaluation.

TABLE 4. 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 post-operative hypocalcemia (or hypocalcemia of any cause). 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 rule out (or in) 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 is used for severe hypomagnesemia. Both 10% and 50% solutions of magnesium sulfate are available. A common regimen is 2-4 mls IV of a 50% (48 mgs) solution given over 10-15 minutes followed by similar amounts given daily. Several days of treatment are usually required to restore magnesium status. The objective of chronic therapy is to keep the patient free of symptoms and to maintain serum calcium of approximately 8.0-9.0 mg/dL. With lower serum calcium levels, the patient may not only experience symptoms but may be predisposed over time to cataracts. 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 may predispose to nephrolithiasis, nephrocalcinosis, and renal damage.

Chronic hypocalcemia. Calcium and vitamin D are used to treat most cause of chronic hypocalcemia, like 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. Calcitrol is the preferred preparation of vitamin D, since it is rapidly active and has a short half-life (i.e., rapidly reversible) in contrast to the other forms of vitamin D **(Table 5).** In patients with renal failure, treatment is directed at maintaining normal levels of calcium, phosphorus, and the calcium-phosphorus product and the intact PTH within an acceptable range for the chronic kidney disease. 1,25 dihydroxyvitamin D or calcitriol or one of its analogs can be given orally or parenterally. Vitamin D may be used for nutritional deficiency.

Table 5. Vitamin D preparations for hypocalcemia treatment.

Name	Daily dose	Time for-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 for signs and symptoms of recurrence **(Table 1)** and with serum calcium measurements, urinary calcium measurements at less frequent intervals, and for progression of the underlying disease **(Table 2).** Other tests can be conducted as clinically indicated, notably magnesium measurements. 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, 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

NONE APPLICABLE

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