HYPOCALCEMIA - 2008

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Concept: Lower-than-normal blood calcium, or abnormally decreased level of serum calcium below 9.0 mg/100ml (The normal blood calcium range is from 9.0 to 110mg/100ml) or less than 2.2 mmol/L and ionized calcium level of
less than 1.1 mmol/L (The normal range for ionized calcium is 1.13 to 1.32 mmolL mg/dL). Ionized calcium (Ca(2+)) seems to be the best measure of active serum calcium but, numerous laboratories do not have Ca(2+) analyzers. Hypocalcemia, occurs when the concentration of free calcium ions in the blood falls below 4.0mg/dL (dL= one tenth of a liter). The normal concentration of free calcium ions in the blood serum is 4.0–6.0 mg/dL. The level of total calcium in the blood serum is normally 9.5–10.5 mg/dL.
Hypocalcemia is a rare finding and frequently is associated with hypoalbuminemia, hypoparathyroidism, kidney malfunction (chronic renal disease) or vitamin D deficiency. Low blood calcium makes the nervous system highly irritable with tetany (spasms of the hands and feet, muscle cramps, abdominal cramps, and overly active reflexes). Chronic hypocalcemia contributes to poor mineralization of bones, soft bones (osteomalacia) and osteoporosis. In children, hypocalcemia leads to rickets raquitismo and
impaired growth. Food sources of calcium include dairy foods, some leafy green vegetables such as broccoli and collards couve, canned salmon, clams moluscos, oysters ostras, calcium-fortified foods, and tofu. According to
the National Academy of Sciences, adequate intake of calcium is 1 gram daily for both men and women. The upper limit for calcium intake is 2.5 grams daily.

ETIOLOGIES

1) LOOP DIURETICS USE OR ABUSE: The most common adverse drug reactions (ADRs) are dose-related and relate to the effect of loop diuretics on diuresis and electrolyte, balance. Common ADRs include: hyponatremia,
hypokalemia, hypomagnesemia, dehydratation, hyperuricemia, gout, dizziness, postural hypotension, syncope. Infrequent ADRs include: dyslipidemia, increased serum creatinine concentration, hypocalcemia, rash. Ototoxicity is a serious, but rare ADR associated with use of loop diuretics. This may be limited tinnitus and vertigo, but may result in deafness in serious cases.
Loop diuretics may also precipitate renal failure in patients concomitantly taking an NSAID and anACE inhibitor -- the so-called "triple whammy" effect.

2) DURING MASSIVE TRANSFUSION: hypocalcemia is a well-recognized complication of massive blood transfusion. In theses cases hypomagnesemia may also cause prolongation of the QT interval and should also be considered in the differential diagnosis as the QT interval lengthens. Both hypocalcemia and hypomagnesemia are recognized complications of massive transfusion and both may give rise to a prolonged QT interval. Therefore, if
the QT interval prolongs in association with massive transfusion, both possibilities should be considered. (Meikle A Brian Milne B, Management of prolonged QT interval during a massive transfusion: calcium, magnesium or
both? Canadian Journal of Anesthesia 2000; 47:792-795.)

3) OSTEOMALACIA

4) CHRONIC RENAL FAILURE

5) Hungry bone syndrome: Rapid correction of severe and prolonged hyperparathyroidism (HPT) by surgical parathyroidectomy (PTX) occasionally causes a so-called "hungry bone syndrome" usually secondary or tertiary HPT
related to renal failure. Serum calcium is rapidly taken from the circulation and deposited into the bone. The syndrome is

characterized by prolonged hypocalcemia with hypocalcemic symptoms, as well as a usually mild decrease of serum phosphate. (Nowack R, Wachtler P. Hypophosphatemia and hungry bone syndrome in a dialysis patient with secondary hyperparathyroidism treated with cinacalcet--proposal for an improved monitoring. Clin Lab. 2006;52:583-587.). Much less often, hungry bone syndrome is seen in patients after correction of long-standing metabolic acidosis or after thyroidectomy for hyperthyroidism.

6) RESPIRATORY ALKALOSIS

7) HYPOPARATHYROIDISM: is most common cause of hypocalcemia and is often caused by surgery in the central neck that requires radical resections because of head and neck cancers. It develops in 1% to 2% of patients after
total thyroidectomy for thyroid cancer or benign thyroid disease.1 can result in hypocalcemia, and it commonly is diagnosed during the workup for hypocalcemia.

8) AUTOIMMUNE HYPOPARATHYROIDISM: can be seen as an isolated defect or as part of polyglandular autoimmune syndrome type I, in association with adrenal insufficiency and mucocutaneous candidiasis. Most of these patients have autoantibodies directed against the calcium-sensing receptor.

9) DIGEORGE SYNDROME: congenital hypoparathyroidism associated with hypoplasia or aplasia of parathyroid glands.

10) 22Q11 MICRODELETION SYNDROME: screening for 22q11 deletion should be performed when confronted to hypocalcemic cardiomyopathy or left ventricular systolic dysfunction in conotruncal defects in neonates. (Goulet M, Rio M, Jacquette A, et al. Neonatal hypocalcaemic dilated myocardiopathy due to a 22q11 microdeletion Arch Mal Coeur Vaiss. 2006;99:520-522.);

11) PSEUDOHYPOPARATHYROIDISM: It is is a very rare disease defined as a form of end-organ resistance to PTH Pseudohypoparathyroidism Ia (PHP Ia) is characterized by

resistance to PTH and many other stimuli because of deficiency of stimulatory G protein -subunit. Calcitonin (CT) is a 32-amino acid hormone that is produced by thyroid parafollicular C cells. It reduces plasma calcium levels in acute situations by increasing renal calcium excretion and inhibiting osteoclast-mediated bone resorption. High levels of plasma CT may be found in patients with PHP Ia.

12) ACUTE PANCREATITIS: calcium is precipitated as calcium soaps in the abdominal cavity.

13) USE OF CALCIUM CHELATES: Several medications chelate calcium in the circulation and thus produce hypocalcemia. In these situations, ionized calcium is decreased while total calcium may be normal. These medications include EDTA, citrate (present in transfused blood), lactate, and foscarnet.

14) TRANSIENT POST-TOTAL THYROIDECTOMY HYPOCALCEMIA: Thyroidectomy is a commonly performed operation for the treatment of thyroid disease. Inadvertent removal of parathyroid glands is a recognized complication of this operation and may have consequences on the longterm regulation of calcium homeostasis post-operatively. (Testa A, Fant V, De Rosa A, et al, Calcitriol plus hydrochlorothiazide prevents transient post thyroidectomy hypocalcemia. Horm Metab Res. 2006;38:821-826.) In specialist hands there is a risk of removing a single parathyroid gland of approximately 17% during thyroid surgery. However, this does not appear to carry a risk of causing hypocalcaemia post-operatively. Careful capsular dissection will reduce the incidence of removing more than one gland;

15) EXTENSIVE OSTEOBLASTIC SKELETAL METASTASES: especially from prostate and breast cancer, may also lead to hypocalcemia. (Dawson SJ, Murray RM,
Rischin D. Hypocalcemia associated with bone metastases in a patient with salivary-gland carcinoma.Nat Clin Pract Oncol. 2006;3:104-107.);

16) CHEMOTHERAPY: Patients receiving chemotherapy, including cisplatin, 5-fluorouracil, and leucovorin develop hypocalcemia mediated through hypomagnesemia.

17) AFTER SURGERIES: Low serum calcium levels seen in patients after surgeries can be mediated by the citrate content of transfused blood or by large fluid administration and hypoalbuminemia.

18) SEPSIS: Patients with sepsis demonstrate hypocalcemia that is usually associated with hypoalbuminemia.

CLINICAL PRESENTATION OF HYPOCALCEMIA

Hypocalcemia can present as an asymptomatic laboratory finding or as a severe, life-threatening condition (Table 1). In the setting of acute hypocalcemia, rapid treatment may be necessary. In contrast, chronic hypocalcemia may be well tolerated, but treatment is necessary to prevent long-term complications.

Clinical Features Associated With Hypocalcemia

Neuromuscular inability

The hallmark of acute hypocalcemia is neuromuscular irritability:

- Chvostek's sign
- Trousseau's sign
- Paresthesias
- Tetany
- Seizures (focal, petit mal, grand mal)
- Fatigue
- Anxiety
- Muscle cramps
- Polymyositis
- Laryngeal spasms
- Bronchial spasms

Neurological signs and symptoms

- Extrapyramidal signs due to calcification of basal ganglia
- Calcification of cerebral cortex or cerebellum

- Personality disturbances
- Irritability
- Impaired intellectual ability
- Nonspecific EEG changes
- Increased intracranial pressure
- Parkinsonism
- Choreoathetosis
- Dystonic spasms

Mental status

- Confusion
- Disorientation
- Psychosis
- Psychoneurosis

Ectodermal changes

- Dry skin
- Coarse hair
- Brittle nails
- Alopecia
- Enamel hypoplasia
- Shortened premolar roots
- Thickened lamina dura
- Delayed tooth eruption
- Increased dental caries
- Atopic eczema
- Exfoliative dermatitis
- Psoriasis
- Impetigo herpetiformis

Smooth muscle involvement

- Dysphagia
- Abdominal pain
- Biliary colic
- Dyspnea
- Wheezing

Ophthalmologic manifestations

- Subcapsular cataracts
- Papilledema

Cardiac features

- Prolonged QT interval in ECG

- Congestive heart failure
- Reversible cardiomyopathy

Adapted from Fitzpatrick, L.A.: The hypocalcemic states. Disorders of Bone and Mineral Metabolism. M. Favus (ed), Lippincott Williams & Wilkins, Philadelphia, PA, pp. 568-588, 2002.

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Cardiovascular manifestations may be present as a sign or symptom of hypocalcemia

Electrocardiographic features

The ventricular recovery time, as represented on the ECG by the QTc interval, is altered by the extremes of serum calcium levels:
Deficiency-------Hypocalcemia------Prolonged QTc interval.
Excess-------Hypercalcemia--------Shortened QTc interval.
The change in the QTc interval is produced by an increase or decrease in the ST segment while the T wave remain relatively normal. The typical ECG pattern of hypocalcemia consists of QT prolongation due to ST segment prolongation. The QTc rarely exceeds 140% of normal. If QTc exceeds that number, the U wave is likely to be included in the measurement.
A pattern of acute anteroseptal injury on ECG without infarction has been associated with hypocalcemia and after electrolyte abnormalities.
T-waves are abnormal in approximately 50% of patients. The T wave is usually of normal width but can be narrow based if there is coexistent (moderate) hyperkalemia. Hypocalcemia per se does not produce T wave inversion. When present, the latter is usually a reflection of coexisting processes such as LVE and incomplete LBBB. A very marked subendocardial ischemia (with the so-called hyperacute ST-T changes) can produce a similar pattern, but in those cases the T wave, though peaked, is not as narrow based. Similarly, hypocalcemia in association with a terminal wave consisting of both the T and the U waves. While the ST segment is prolonged, the total QU interval

remains normal.
An ECG pattern similar to that of hypocalcemia can be produced by organic abnormalities of the central nervous system and by congenitally prolonged QT intervals such as the LQT3, LQT8 (Timothy syndrome) and LQT9 variants.
Torsade de Pointes tendency secondary to QT prolongation
Atrioventricular block are sometimes observed.
Hypomagnesemia in concert with hypocalcemia may magnify the EGG abnormalities. Rarely congestive heart failure may occur
Reversible cardiomyopathy due to hypocalcemia has been reported; In patients with mild, asymptomatic hypocalcemia, improved cardiac output, peak velocity of blood flow, exercise tolerance, and ascending aortic resistance are improved with calcium replacement.