Section 7

Metabolic and hematological disorders

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28 Hypocalcemia

Hypocalcemia is a common clinical and laboratory abnormality in neonates. Ionized calcium is essential for many biological processes including coagulation, neuromuscular functioning, integrity of cell membrane, and many cellular enzymatic reactions.

Calcium homeostasis during fetal and neonatal period

Calcium (Ca) is actively transferred from mother to fetus during last trimester as demonstrated by a significantly higher level of total Ca concentration in cord blood compared to maternal serum.[1] Serum Ca (SCa) in the fetus is 10 to 11 mg/dL at term gestation that maintains a gradient of maternal-to-fetal calcium of 1 : 1.4. Parathyroid hormone (PTH) and calcitonin (CT) do not cross the placental barrier. PTH related peptide (PTHrP) is the main regulator of the positive Ca balance across the placenta. Although vitamin D is critical factor for mineral ion homeostasis and bone development during adult life, fetal mineral ion homeostasis is mostly independent of this hormone.

After birth, the SCa levels in neonates depend on PTH secretion, dietary calcium intake, renal calcium reabsorption, and skeletal calcium and vitamin D status. Hence, after delivery, SCa levels start decreasing, the rate and extent of decrease is inversely proportional to the gestation, and reaches a nadir of 7.5 to 8.5 mg/dL in healthy term neonates by day 2 of life. This transition phase is responsible for the increased risk of early-onset hypocalcemia in high-risk neonates. This postnatal drop in SCa may be related to decreased PTH level, end-organ unresponsiveness to PTH[2], abnormalities of vitamin D metabolism, hyperphosphatemia, hypomagnesemia, and hypercalcitonemia.[3] PTH levels increase gradually in the first 48 hours of life and normal levels of SCa are achieved by 3rd to 4th day of life.[4] Efficacy of the intestinal absorption and the renal handling of Ca mature by 2 to 4 weeks of birth.

Distribution of calcium in the body

Body Ca exists in two major compartments: skeleton (99%) and extracellular fluid (1%). Ca in the extracellular fluid is present in three forms[5] - bound to albumin (40%), bound to anions like phosphorus, citrate, sulfate and lactate (10%), and as free ionized form (50%). Ionized serum calcium (iSCa) is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity.

Measurement of the total serum Ca (tSCa) concentration alone can be misleading because the relationship between tSCa and iSCa is not always linear. Correlation between two is poor when the serum albumin concentration is low and, to a lesser degree, with disturbances in acid-base status, both of which occur frequently in premature or sick infants. With hypoalbuminemia, tSCa is low while iSCa is normal. Falsely low iSCa may be recorded in alkalosis and with heparin contamination of blood sample. In general, the tSCa falls by 0.8 mg/dL (0.2 mmol/L) for every 1.0 g/dL fall in the plasma albumin concentration. *Therefore, estimation of tSCa is a poor substitute for measuring the iSCa. For 0.1 unit ↑ in pH 0.16 mg/dL ↓ in ionised Ca.*

Definition

Hypocalcemia is defined by different tSCa and iSCa cutoffs for preterm and term infants (Table 28.1).[6]

Table 28.1: Definition of hypocalcemia

Gestation	Total serum calcium	Ionic serum calcium
Preterm	<7 mg/dL (1.75 mmol/L)	<4 mg/dL (1 mmol/L)
Term	<8 mg/dL (2 mmol/L; total)	<4.8 mg/dL (1.2 mmol/L)

SCa is usually reported in different units viz. mg/dL, mEq/L and mmol/L. The relationship between these units is related to the following equations:

mmol/L = [mg/dL x 10] ÷ molecular wt

mEq/L = mmol/L x valency

Since the molecular weight of Ca is 40 and the valence is +2, 1

mg/dL is equivalent to 0.25 mmol/L and to 0.5 mEq/L. Thus, values in mg/dL may be converted to molar units (mmol/L) by dividing it by 4.

Hypocalcemia is usually classified into two categories based on the age of onset. Early-onset hypocalcemia (ENH) presents within first 72 -96 hours and usually requires short-term calcium supplementation. In contrast, late onset hypocalcemia (LNH) usually presents after 96 hours and requires long-term therapy.

Early onset neonatal hypocalcemia (ENH)

This condition is fairly common and seen within the first 3 to 4 days of life in following clinical settings (Panel 1):

Panel 1: Causes of early onset hypocalcemia

Prematurity
Preeclampsia
Infant of diabetic mother (IDM)
Perinatal stress/ asphyxia
Maternal intake of anticonvulsants (phenobarbitone, phenytoin sodium)
Maternal hyperparathyroidism
Iatrogenic (alkalosis, use of blood products, diuretics, phototherapy, lipid infusions etc)

Prematurity: Hypocalcemia may be related to premature termination of transplacental supply, exaggeration of the postnatal drop to hypocalcemic levels, increased calcitonin and diminished target organ responsiveness to parathyroid hormone in very preterm infants.

Infants of diabetic mother (gestational and insulin dependent): This may be related to increased calcium demands of a macrosomic baby.[8] Magnesium depletion in mothers with diabetes mellitus causes hypomagnesemic state in the fetus. Hypomagnesemia induces functional hypoparathyroidism and hypocalcemia in the infant. A high incidence of birth asphyxia and prematurity in IDM are the other contributing factors.

Perinatal asphyxia: Delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load (due to tissue catabolism) renal insufficiency, and diminished parathyroid hormone secretion may contribute to hypocalcemia in neonates with asphyxia.

Maternal hyperparathyroidism: This causes intrauterine hypercalcemia suppressing the parathyroid activity in the fetus resulting in impaired parathyroid responsiveness to hypocalcaemia after birth. Hypocalcaemia may be severe and prolonged.

Maternal anticonvulsants: Intake of anticonvulsants like phenobarbitone and phenytoin alters the vitamin D metabolism and predisposes them to its deficiency. The infants of epileptic mothers may be at risk of neonatal hypocalcemia. It can be prevented by vitamin D supplementation to mothers during pregnancy.

Iatrogenic: Any condition causing alkalosis increases the binding of the calcium with albumin and causes decrease in iSCa.

We do not routinely screen neonates for ENH.

Clinical presentation

Asymptomatic: ENH is usually asymptomatic LNH and is incidentally detected.

Symptomatic: The symptoms may be of neuromuscular irritability - myoclonic jerks, jitteriness, exaggerated startle, and seizures. They may represent the cardiac involvement like tachycardia, heart failure, prolonged QT interval, and decreased contractibility. More often they are non-specific and not related to the severity of hypocalcemia. Apnea, cyanosis, tachypnea, vomiting and laryngospasm are other symptoms that are noted.

Diagnosis

Laboratory: by measuring total or ionized SCa. Ionized calcium is the preferred mode for diagnosis of hypocalcemia.
ECG: QoTc >0.22 seconds or QTc >0.45 seconds

$$QTc = \frac{\text{QT interval in seconds}}{\text{R-R interval in seconds}}$$

$$\text{Qo}Tc = \frac{\text{Qo T interval in seconds}}{\text{R-R interval in seconds}}$$

(QT interval is measured from origin of q wave to end of T wave on ECG; Qo T is measured from origin of q wave to origin of T wave).

A diagnosis of hypocalcemia based only on ECG criteria is likely to yield a high-false positive rate. Although these parameters have good correlation with hypocalcaemia in low birth weight infants (sensitivity of 77% and specificity of 94.7%)[9]. Neonates suspected to have hypocalcemia by ECG criteria should have the diagnosis confirmed by measurement of serum calcium levels.

Treatment of early onset hypocalcemia

***Patients diagnosed to have asymptomatic hypocalcemia*:** Infants detected to have hypocalcemia on screening and who are otherwise asymptomatic should receive 80 mg/kg/day of elemental calcium (8 mL/kg/day of 10% calcium gluconate; 1 mL=9.4 mg of elemental calcium) for 48 hours. This may be tapered to 50% dose for another 24 hours and then discontinued. Neonates tolerating oral feeds may be treated with oral calcium (IV preparation may be used orally).

***Patients diagnosed to have symptomatic hypocalcemia*:** These patients should receive a bolus dose of 2 mL/kg diluted 1:1 with 5% dextrose over 10 minutes under cardiac monitoring. When there is severe hypocalcaemia with poor cardiac function, calcium chloride 20 mg/kg may be given through a central line over 10-30 minutes (because calcium chloride, unlike gluconate salt, does not require metabolism by the liver for the release of free calcium). This should be followed by continuous IV infusion of 80 mg/kg/day elemental calcium for 48 hours. Continuous infusion is preferred to IV bolus doses (1 mL/kg/dose q 6 hourly). Calcium infusion should be dropped to 50% of the original dose for the next 24 hours and then discontinued. Normal calcium values should be documented at 48 hours before weaning the infusion.The infusion may be replaced with oral calcium therapy on the last day.

All categories of hypocalcemia should be treated for at least 72 hours. Continuous infusion is preferred to IV bolus doses. Symptomatic hypocalcemia should be treated with a continuous infusion for at least 48 hours.

Precautions and side effects

Bradycardia and arrhythmia are known side effects of bolus IV calcium administration. Hence, bolus doses of calcium should be diluted 1:1 with 5% dextrose and given slowly over 10 to 30 minutes under cardiac monitoring. An umbilical venous catheter (UVC) may be used for administration of calcium only after ensuring that the tip is positioned in the inferior vena cava. Hepatic necrosis may occur if the tip of the UVC lies in a branch of the portal vein. Umbilical artery catheter (UAC) should never be used for giving calcium injections. Accidental injection into the umbilical artery may result in arterial spasms and intestinal necrosis.

Skin and subcutaneous tissue necrosis may occur due to extravasation. Hence, IV sites where calcium is being infused should be checked at least q2 hour to monitor for extravasation.

Prolonged or resistant hypocalcemia

This condition should be considered in the following situations:

- Symptomatic hypocalcemia unresponsive to adequate doses of calcium therapy
- Infants needing calcium supplements beyond 72 hours of age
- Hypocalcemia presenting at the end of the first week.

These infants should be investigated for causes of LNH (see below).

Late onset neonatal hypocalcemia (LNH)

It usually presents at the end of the first week of life. It is usually symptomatic in the form of neonatal tetany or seizures and is caused by high phosphate intake (iatrogenic) (Table 28.2).

Table 28.2: Causes of late onset hypocalcemia

1. Increased phosphate load: cow milk, renal insufficiency
2. Hypomagnesemia
3. Vitamin D deficiency
4. Maternal vitamin D deficiency
5. Malabsorption
6. Hepatobiliary disease
7. PTH resistance
8. Transient neonatal pseudo-hypoparathyroidism
9. Hypoparathyroidism
   a) *Primary: hypoplas*ia/aplasia (Di George's syndrome, CATCH 22 syndrome), a*ctivating* mutations of the calcium sensing receptor (CSR)
   b) *Secondary: maternal hy*perparathyroidism, *metabolic sy*ndromes (*Kenny-caffey* syndrome, *long-chain f*atty acyl CoA dehydrogenase deficiency, *Kearns-sayre* syndrome
10. Autosomal dominant hypocalcemic hypercalciuria
11. Iatrogenic: Citrated blood products, lipid infusion, bicarbonate therapy, loop diuretics, glucocorticoids, phosphate therapy, aminoglycosides (mainly gentamicin), viral gastroenteritis.

Examination

Neonates with LNH should be examined with special emphasis on presence of cataracts, hearing, and any evidence of basal ganglia involvement (movement disorder) in the follow up.

Investigations

Investigations listed in Table 28.3 should be considered in LNH or if the hypocalcemia does not respond to adequate doses of calcium.

If hypocalcemia is present with hyperphosphatemia and a normal renal function, hypoparathyroidism should be strongly suspected (See Table 28.4 for interpretation of diagnostic investigation.)

Table 28.3: Investigations required in infants with persistent / late onset hypocalcaemia

First line	Second line	Others
Serum phosphate Serum alkaline phosphatase (SAP) Liver function tests Renal function tests (RFT) X ray chest/ wrist Arterial pH	Serum magnesium (Mg) Serum parathormone levels (PTH) 25-hydroxyvitamin D levels (25-OH D) Urine calcium creatinine ratio Maternal calcium, phosphate, and alkaline phosphatase	Serum magnesium Serum parathormone levels (PTH) Urine calcium creatinine ratio Maternal calcium, phosphate, and alkaline phosphatase

Table 28.4 Interpretation of investigations

Disorder causing hypocalcaemia	Findings
Hypoparathyroidism	High: phosphate Low: SAP, PTH, 25-OH D
Pseudo-hypoparathyroidism	High: SAP, PTH, Phosphate Low: 25-OH D
Chronic renal failure	High: phosphate, SAP, PTH deranged RFT Low: 25-OH D, pH (acidotic)
Hypomagnesemia	High: PTH Low: phosphate, Mg, 25-OH D
VDDR*1	High: SAP, PTH Low: Phosphate, 25-OH D
VDDR* II	High: SAP, 25-OH D,PTH Low: Phosphate

(*VDDR: Vitamin D dependent rickets)

Treatment of LNH

The initial treatment of LNH is same as that of ENH. This should be followed by specific management according to the etiology and may be life-long in certain diseases.

1. ***Hypomagnesemia:*** Symptomatic hypocalcemia unresponsive to adequate doses of IV calcium therapy is usually due to hypomagnesemia. It may present either as ENH or LNH. The neonate should receive two doses of 0.2 mL/kg of 50% $MgSO_4$ injection, 12 hours apart, deep IM

followed by a maintenance dose of 0.2 mL/kg/day of 50% $MgSO_4$ orally for 3 days.

2. ***High phosphate load:*** These infants have hyperphosphatemia with near-normal calcium levels. This results from feeding of animal milk which contain high phosphate load (e.g. cow's milk). Exclusive breastfeeding should be encouraged and animal milk should be discontinued, if possible. Phosphate binding gels must be avoided.
3. ***Hypoparathyroidism:*** These infants have high phosphate and low calcium levels in the blood and *normal renal function*. High phosphate levels in the absence of high phosphate intake (cow's milk) and normal renal functions indicate towards hypoparathyroidism.[10]
   If phosphate level is high, addition of calcium may lead to calcium deposition and tissue damage. Thus, reduction in the phosphate level must be attempted in order to keep the calcium and phosphate product (CaxP) less than 55.[11] These neonates should be supplemented with calcium (50 mg/kg/day in 3 divided doses) and 1,25 $(OH)_2$ vitamin D_3. Therapy may be stopped in hypocalcemia secondary to maternal hyperparathyroidism after 6 weeks.
4. ***Vitamin D deficiency states:*** These babies have hypocalcemia associated with hypophosphatemia due to an intact parathormone response on the kidneys. They benefit from 1, 25 $(OH)_2$ vitamin D_3 supplementation in a dose of 30-60 ng/kg/day.

Neonates with LNH are to be monitored for SCa, phosphate, 24-hour urinary calcium, and calcium-creatinine ratio after starting treatment. Try to keep the calcium in the lower range as defective distal tubular absorption leads to hypercalciuria and nephrocalcinosis.[12]

Prognosis and outcome

Most cases of ENH resolve within 48-72 hours without any clinically significant sequelae. LNH secondary to exogenous phosphate load and magnesium deficiency also responds well to phosphate restriction and magnesium repletion. When caused by hypoparathyroidism, hypocalcemia requires

continued therapy with vitamin D and calcium. The period of therapy depends on the nature of the hypoparathyroidism, which can be transient, last several weeks to months, or be permanent.

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