Hypocalcemia in the Newborn

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Abstract

Hypocalcaemia is a frequently observed clinical and laboratory abnormality in neonates. Ionic calcium is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity, and many of the cellular enzymatic activities. Healthy term infants undergo a physiological nadir in serum calcium levels by 24-48 hours of age. This nadir may drop to hypocalcemic levels in high-risk neonates including infants of diabetic mothers, preterm infants and infants with perinatal asphyxia. The early onset hypocalcemia which presents within 72 hours requires treatment with calcium supplementation for at least 72 hours. In contrast, late onset hypocalcemia usually presents after 7 days and requires longer term therapy.

Keywords: Hypocalcemia, Newborn, Therapy

Introduction

During the last trimester, calcium is actively transferred from mother to the fetus as demonstrated by a significantly high level of total calcium concentration in cord blood compared to maternal serum.[1] Parathyroid hormone (PTH) and calcitonin (CT) do not cross the placental barrier. The PTH related peptide (PTHrP) is the main regulator of the positive calcium balance across the placenta. Serum calcium (SCa) in the fetus is 10-11 mg/dL at term (1-2 mg higher as compared to mother).

After birth the SCa levels in newborns depend on the PTH secretion, dietary calcium intake, renal calcium reabsorbtion, skeletal calcium stores, and vitamin D status. Hence, after delivery, calcium levels start decreasing (the rate and extent of decrease is inversely proportional to the gestation) and reaches a nadir of 7.5-8.5 mg/dL in healthy term babies by day 2 of life. This drop in postnatal SCa may be related to hypoparathyroidism, end organ unresponsiveness to parathyroid hormone [2], abnormalities of vitamin D metabolism, hyperphosphatemia, hypomagnesemia, and hypercalcitonemia[3] which occurs by 12-24 hours of age. PTH levels increase gradually in the first 48 hours of life and normal levels of SCa are regained by 3rd day of life.[4] The efficacy of the intestinal absorption of calcium and the renal handling matures by 2 to 4 weeks. This transition phase is responsible for the increased risk of early onset hypocalcemia in high-risk neonates.

Calcium homeostasis in newborn

Body calcium exists in two major compartments: skeleton (99%) and extracellular fluid (1%). Calcium in the extracellular fluid is present in three forms: (a) bound to albumin (40%) (b) bound to anions like phosphorus, citrate, sulfate and lactate (10%) and (c) free ionized form (50%)[5]. Ionized calcium 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 concentration alone can be misleading because the relationship between total and ionized Ca is not always linear. Correlation is poor when the serum albumin concentration is low or, to a lesser degree, with disturbances in acid-base status, both of which occur frequently in premature or sick infants. With hypoalbuminemia, the total Ca concentration will be low while the ionized fraction will be normal unless some other factor is affecting Ca metabolism. More so, falsely low ionic calcium levels may be recorded in alkalosis and with heparin use.

In general, the plasma calcium concentration 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 total calcium levels is a poor substitute for measuring the ionized levels.

Definition

Hypocalcemia is defined as total serum calcium of less than 7 mg/dL (1.75 mmol/L) or ionized calcium less than 4 mg/dL (1 mmol/L) in preterm infants

and less than 8 mg/dL (2 mmol/L; total) or <1.2 mmol/L (ionic) in term neonates.[6]

The SCa concentration is usually reported in different ways 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 calcium 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 by 4.

Early onset neonatal hypocalcemia (ENH)Table 1

This condition is fairly common and seen within the first 3-4 days of life in following clinical settings:

Prematurity: This may be related to premature termination of trans-placental supply, exaggeration of the postnatal drop to hypocalcemic levels, increased calcitonin and diminished target organ responsiveness to parathyroid hormone.

Infant of diabetic mother (gestational and insulin dependent): This may be related to increased calcium demands of a macrosomic baby.[7] Magnesium depletion in mothers with diabetes mellitus causes hypomagnesemic state in the fetus. This hypomagnesemia induces functional hypoparathyroidism and hypocalcemia in the infant. A high incidence of birth asphyxia and prematurity in infants of diabetic mothers are also contributing factors.

Perinatal asphyxia: Delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load, renal insufficiency, and

diminished parathyroid hormone secretion all may contribute to hypocalcemia.

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.

Intrauterine growth restriction (IUGR): Infants with IUGR may have hypocalcemia if they are born preterm and/or have had perinatal asphyxia. ***Small for gestational age is not an independent risk factor for ENH***.

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

Screening is recommended in at risk neonates

1.Preterm infants born before 32 wks

2. Infants of diabetic mothers on iv fluids

3.Infants born after severe perinatal asphyxia defined as Apgar score < 4 at 1 minute of age

Time schedule for screening

At 24 and 48 hours of age in at risk babies

Clinical presentation:

1. ***Asymptomatic:*** ENH is usually asymptomatic unlike the late onset variety and is incidentally detected.

2. ***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, decreased contractibility. More often they are non-specific and not related to the severity of hypocalcemia. Apnea, cyanosis, tachypnoea, vomiting and laryngospasm are other symptoms that are noted.

Diagnosis

1. ***Laboratory:*** Total or ionized serum calcium (total <7 mg/dL or ionized <4.0 mg/dL). Ionized calcium is the preferred mode for diagnosis of hypocalcemia.
2. ***ECG:*** QoTc >0.22 seconds or QTc >0.45 seconds

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

$$QoTc = \frac{\text{QoT interval in seconds}}{\sqrt{\text{R-R interval in seconds}}}$$

(QT interval is measured from origin of q wave to end of T wave on ECG; QoT 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%)[8], neonates suspected to have hypocalcemia by ECG criteria should have the diagnosis confirmed by measurement of serum calcium levels.

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Treatment of early onset hypocalcemia

(1 ml of calcium gluconate (10%) gives 9 mg of elemental calcium)

1. ***Patients at increased risk of hypocalcemia(prophylactic)****:* Preterm infants (≤32 weeks), sick infants of diabetic mothers and those with severe perinatal asphyxia should receive 40 mg/kg/day of elemental calcium (4 mL/kg/day of 10% calcium gluconate) for prevention of early onset hypocalcemia. However there is not sufficient evidence for this practice. Infants tolerating oral feeds may receive this calcium orally q 6 hourly. Therapy should be continued for 3 days. Oral calcium preparations have high osmolality and should be avoided in babies at higher risk of necrotizing enterocolitis.
2. ***Patients diagnosed to have asymptomatic hypocalcemia(on screening)***: Infants detected to have hypocalcemia on screening and who are otherwise asymptomatic should receive 80-mg/kg/day elemental calcium (8 mL/kg/day of 10% calcium gluconate) 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).

3. ***Patients diagnosed to have symptomatic hypocalcemia***: These patients should receive a bolus dose of 2 mL/kg/dose 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 (as chloride in comparison to gluconate does not require the metabolism by the liver for the release of free calcium). This should be followed by a 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. The infusion may be replaced with oral calcium therapy on the last day. Normal calcium values should be documented at 48 hours before weaning the infusion.

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. (refer Algorithm 1)

Algorithm 1

Management of early neonatal hypocalcaemia

Hypocalcemia
Total serum Cal <7 mg/dl

Asymptomatic

80 mg/kg/day for 48 hrs
(8 mL/kg/day of 10% calcium gluconate)

⇩

Taper to 40 mg/kg/day for one day
Then stop

Symptomatic

Bolus of 2 mL/kg calcium gluconate 1:1 diluted with 5 % dextrose over 10 minutes under cardiac monitoring

⇩

Followed by continuous infusion 80 mg/kg/day for 48 hrs
(8 mL/kg/day of 10% calcium gluconate)
Document normal calcium at 48 hrs

⇩

Then taper to 40 mg/kg/day for one day
Then stop

Prophylactic

Preterm< 32 wks, sick IDM, severe asphyxia
40 mg/kg/day for 3 days
(4ml/kg/day of 10% calcium gluconate)
IV or oral if can tolerate per oral

- *Treatment is for 72 hours*
- *Continuous infusion is better than bolus*
- *Symptomatic babies treatment is 48 hrs continuous infusion*

In case the hypoclcemia does not correct by the above by, 72 hours than investigate for causes of late hypocalcemia.- Refer Table 2

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 UAC 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 q 2 hourly to monitor for extravasation and avoid subcutaneous tissue necrosis.

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)

This condition is rare as compared to ENH. It usually presents at the end of the first week of life. It is usually symptomatic in the form of neonatal tetany or seizures. This is usually caused by high phosphate intake (iatrogenic). The causes are listed in table 2.

Examination:

Such babies should have an examination with special emphasis on cataracts, hearing, and any evidence of basal ganglia involvement (movement disorder).

Investigations

These should be considered in LNH or if the hypocalcemia does not respond to adequate doses of calcium. The work up of such a case is very important to determine the etiology. The same can be planned as per the table 3.

If hypocalcemia is present with hyperphosphatemia and a normal renal function, hypoparathyroidism should be strongly suspected

Treatment of LNH

The treatment of LNH is specific to etiology and may in certain diseases be life-long.

1. ***Hypomagnesemia:*** Symptomatic hypocalcemia unresponsive to adequate doses of IV calcium therapy is usually due to hypomagnesemia. It may present either as ENH or later as LNH. The neonate should receive 2 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% $MgSO_4$, PO for 3 days.

2. *High phosphate load:* These infants have hyperphosphatemia with near normal calcium levels. Exclusive breast-feeding should be encouraged and top feeding with cow's milk should be discontinued. Phosphate binding gels should be avoided.

3. *Hypoparathyroidism[9]* These infants tend to be hyperphosphatemic and hypocalcemic with normal renal function. Elevated phosphate levels in the absence of exogenous phosphate load (cow's milk) and presence of normal renal functions indicates parathormone inefficiency. It is important to realize that if the phosphate level is very high, then adding calcium will lead to calcium deposition and tissue damage. Thus attempts should be made to reduce the phosphate (so as to keep the calcium and the phosphate product less than 55)[10]. These neonates need supplementation with calcium (50 mg/kg/day in 3 divided doses) and $1,25(OH)_2$ Vitamin D_3 (0.5-1 μg/day). Syrups with 125 mg and 250 mg per 5ml of calcium are available.$1,25(OH)_2$ vitamin D_3 (calcitriol) is available as 0.25 μg capsules. 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 Vitamin D_3 supplementation in a dose of 30-60 ng/kg/day

Monitoring

The baby is monitored for the SCa, and phosphate, 24 hour urinary calcium, and calcium creatinine ratio. Try to keep the calcium in the lower range as defective distal tubular absorption leads to hypercalciuria and nephrocalcinosis.[11]

Prognosis and outcome

Most cases of early neonatal hypocalcemia resolve within 48-72 hours without any clinically significant sequelae.

Late neonatal hypocalcemia 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 metabolites and calcium salts. 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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Table 1 Causes of early onset hypocalcaemia
• Prematurity • Preeclampsia • Infant of Diabetic mother • Perinatal stress/ asphyxia • Maternal intake of anticonvulsants (phenobarbitone, phenytoin sodium) • Maternal hyperparathyroidism • Iatrogenic (alkalosis, use of blood products, diuretics, phototherapy, lipid infusions etc)

Table 2 **Causes of late onset hypocalcemia**

- ***Increased phosphate load***
  Cow milk, renal insufficiency
- ***Hypomagnesemia***
- ***Vitamin D deficiency***
  Maternal vitamin D deficiency
  Malabsorption
  Renal insufficiency
  Hepatobiliary disease
- ***PTH resistence***
  Transient neonatal pseudohypoparathyroidism
- ***Hypoparathyroidism***
  Primary
  Hypoplasia, aplasia of parathyroid glands - (Di George's syndrome), CATCH 22 syndrome (cardiac anomaly, abnormal facies, thymic aplasia, cleft palate, hypocalcaemia with deletion on chromosome 22)
  Activating mutations of the calcium sensing receptor (CSR)
  Secondary
  Maternal hyperparathyroidism
- ***Metabolic Syndromes***
  Kenny-caffey syndrome
  Long-chain fatty acyl CoA dehydrogenase deficiency
  Kearns-sayre syndrome
- ***Iatrogenic***
  Citrated blood products
  Lipid infusions
  Bicrbonate therepy
  Diueretics (loop diuretics)
  Glucocorticosteriods
  Phosphate therepy
  Use of Aminoglycosides (mainly gentamicin) as single dose
  Alkalosis
  Phototherapy

Table 3 **Investigations required in infants with persistent / late onset hypocalcaemia**

Investigations required			
	First line Serum phosphate Serum alkaline phosphatase (SAP) Liver function tests Renal function tests X ray chest/ wrist Arterial pH	**Second line** Serum magnesium Serum parathormone levels (PTH) Urine calcium creatinine ratio Maternal calcium, phosphate, and alkaline phosphatase	**Others** CT brain for calcification Echocardiography Vitamin D levels (1,25 D3) Hearing evaluation Serum cortisol Thyroid function tests
S No	***Disorder causing hypocalcaemia***	***Findings***	
1	Hypoparathyroidism	High : Phosphate Low : SAP, PTH, 1,25 D3	
2	Pseudo Hypoparathyroidim	High : SAP, PTH, Phosphate Low : 1,25 D3	
3	Chronic renal failure	High : phosphate, SAP, PTH, pH (acidotic), deranged RFT Low : 1,25 D3	
4	Hypomagnesemia	High : PTH Low : Phosphate, Mg,1,25 D3	
5	VDDR1	High : SAP, PTH Low : Phosphate, 1,25 D3	
6	VDDR II	High : SAP, 1, 25 D3, PTH Low : Phosphate	

(VDDR, vitamin D dependent rickets)