

Hypocalcemia in the Newborn

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ABSTRACT

Healthy term babies undergo a physiological nadir in serum calcium levels by 24-48 hours of age. The nadir may be related to the delayed response of parathyroid and calcitonin hormones in a newborn. 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 long term therapy. Ionized calcium is crucial for many biochemical processes and total serum calcium is a poor substitute for the diagnosis of hypocalcemia. [Indian J Pediatr 2008; 75 (2) : 165-169] E-mail: sdeorari@yahoo.com

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During the 3rd trimester, calcium is transferred from mother to the fetus by active transport as demonstrated by the 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 in the fetus is 10-11 mg/dl at term (1-2 mg higher as compared to mother).

Once the baby is born its calcium levels now depend on the PTH secretion, dietary calcium, renal calcium reabsorption, skeletal calcium stores and vitamin D. Hence, after delivery, calcium levels start decreasing (the rate and extent of decrease being 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 serum calcium may be related to hypoparathyroidism,² end organ unresponsiveness to parathyroid,³ abnormalities of Vit d metabolism, hyperphosphatemia, hypomagnesemia and hypercalcitocalcitonemia⁴ which occurs by 12-24 hours of age. PTH levels increase gradually in the first 48 hours of life and normal levels of serum calcium are regained by 3rd day of life.⁵ The efficacy of the intestinal absorption of

calcium and the renal handling matures at 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; (a) Skeleton (99%) and (b) Extracellular fluid (1%). Calcium in the extracellular fluid is present in 3 forms: (a) bound to albumin (40%) (b) bound to anions like phosphorus, citrate, sulfate and lactate (10%) and (c) free ionized form (50%). 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 plasma 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 ill 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.

In general, the plasma calcium concentration falls by 0.8 mg/dL (0.2 mmol/L) for every 1.0 g/dL (10 g/L) fall in the plasma albumin concentration.

Therefore, estimation of total calcium levels is a poor substitute for measuring the ionized levels.

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DEFINITION

Hypocalcemia is defined as total serum calcium <7 mg/dl or ionized calcium < 4mg/dl.⁶

The serum calcium concentration measured is usually reported in different ways *viz* mg/dL, meq/dL and mmol/dL. The relationship between these units is related to the following equations: mmol/L = [mg/dL × 10] ÷ mol wt, meq/L = mmol/L × valence

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)

This condition is fairly common and seen within the first 3-4 days of life (Table 1).

TABLE 1. Causes of Early Onset Hypocalcemia¹¹

- Prematurity
- Maternal diabetes
- Perinatal stress/ asphyxia
- Maternal intake of anticonvulsants (phenobarbitone, phenytoin sodium)
- Intra uterine growth retardation

Prematurity: Preterm babies born at a gestation ≤32 weeks are at an increased risk of ENH in the first 3 days of postnatal life. This may be related to premature termination of trans-placental supply, exaggeration of the postnatal drop to hypocalcemic levels 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

Perinatal asphyxia: Hypocalcemia and hyperphosphatemia in this condition may be related to renal insufficiency, metabolic acidosis and diminished parathyroid hormone secretion.

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

SMALL FOR GESTATIONAL AGE IS NOT AN INDEPENDENT RISK FACTOR FOR ENH

Screening is recommended in at-risk neonates

1. Preterm infants (≤32 weeks)

2. Infant of diabetic mothers
3. Severe perinatal asphyxia defined as Apgar score <4 at 1 minute of age.

Screening for hypocalcemia is not needed in small for gestational age (SGA) infants unless additional risk factors like asphyxia are present.

Time schedule for screening

At 24 and 48 hours in high-risk babies

CLINICAL PRESENTATION

Asymptomatic : Early onset hypocalcemia is usually asymptomatic unlike the late onset variety and is diagnosed on routine screening.

Symptomatic: The symptoms may be of neuromuscular irritability: myoclonic jerks, jitteriness, exaggerated startle, seizures. They may represent the cardiac involvement like- tachycardia, heart failure, prolonged QT interval, decreased contractility. More often they are non specific nor related to the severity of hypocalcemia. Apnoea, cyanosis, taccypnoea, vomiting and laryngospasm are other symptoms hat are noted.

DIAGNOSIS

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.

ECG: QoTc >0.2 seconds or QTc >0.45 seconds

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

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

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

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

Patients at increased risk of hypocalcemia: Preterm

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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). Infants tolerating oral feeds may receive this calcium orally q 6 hourly. Therapy should be continued for 3 days.

Patients diagnosed to have asymptomatic hypocalcemia: 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).

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. 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.

PRECAUTIONS AND SIDE EFFECTS

Bradycardia and arrhythmia are known side effects of bolus IV calcium administration and bolus doses of calcium should be diluted 1:1 with 5% dextrose and given under cardiac monitoring. An umbilical venous catheter (UVC) may be used for administration of calcium only after ensuring that the tip of the catheter is 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

It is usually symptomatic in the form of neonatal tetany. 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, 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

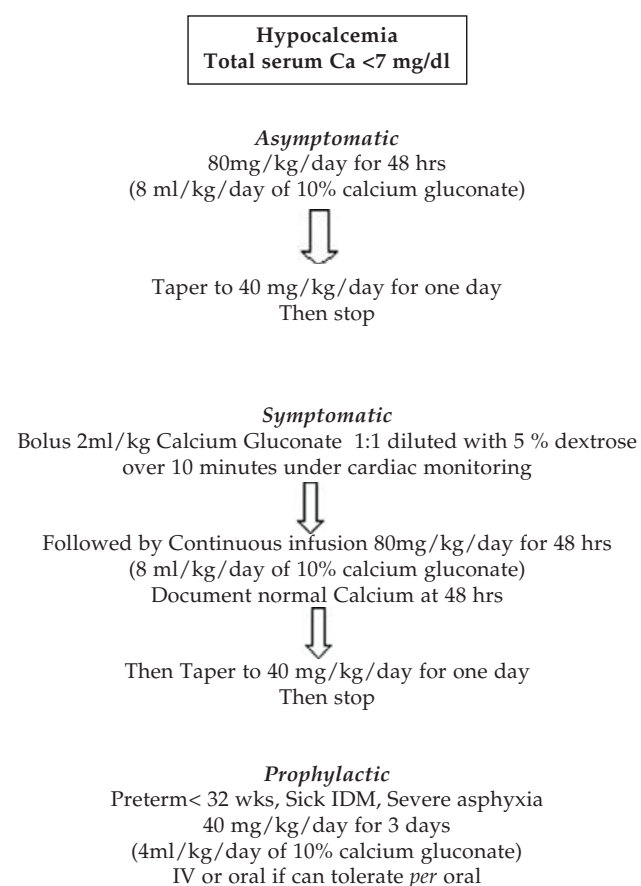
TABLE 2. Causes of Late Onset Hypocalcemia

• Increased phosphate load
Cow's milk, advanced renal insufficiency
• Hypomagnesemia
• Vitamin D deficiency
Maternal vitamin D deficiency
Malabsorption
Renal insufficiency
Hepatobiliary disease
• PTH resistance
Transient neonatal pseudohypoparathyroidism
• Hypoparathyroidism
<u>Primary</u>
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)
<u>Secondary</u>
Maternal hyperparathyroidism
• Metabolic Syndromes
Kenny-caffey syndrome.
Long-chain fatty acyl CoA dehydrogenase deficiency
Kearns-Sayre syndrome
• Iatrogenic
Citrated blood products
Lipid infusions
Bicarbonate therapy
Diuretics (loop diuretics)
Glucocorticosteroids
Phosphate therapy
Alkalosis
Phototherapy

calcium.

- Serum magnesium: Magnesium levels <1.2 mg/dL should be treated
- Serum phosphate (P): Phosphate levels are increased in renal failure, top feeding with cow's milk and hypoparathyroidism.
- Alkaline phosphatase (ALP): ALP levels are increased in hypovitaminosis D
- PTH levels: PTH is decreased in hypoparathyroidism.
- Urine calcium/ creatinine ratio: Ratio >0.2 is suggestive of hypoparathyroidism
- Chest X-ray: Absence of thymus is suggestive of DiGeorge syndrome
- Maternal calcium, phosphate and alkaline phosphatase levels: These would be helpful in detection of maternal vitamin D deficiency

Algorithm for management of neonatal hypocalcaemia



▪ Treatment is for 72 hours

▪ Continuous infusion is better than bolus

▪ Symptomatic babies treatment is 48 hrs continuous infusion

In case the hypocalcemia does not correct by the above by, 72 hours, then investigate for causes of late hypocalcemia as in Table 2.

- A CT scan may be done to look for Basal ganglion calcifications
- An ophthalmic (for cataract) and the hearing evaluation is also important
- An ECHO may be done in case a De George syndrome is suspected

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

TREATMENT OF LNH

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

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% MgSO₄ injection, 12 hours apart, deep IM followed by a maintenance dose of 0.2 mL/kg/day of 50% MgSO₄, PO, 3 days.

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.

Hypoparathyroidism⁹ These infants tend to be hyperphosphatemic and hypocalcemic with normal renal functions. 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 hyperphosphatemia is very high, than adding calcium will lead to calcium deposition and tissue damage, thus attempts should be made to reduce the phosphate (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 D₃ (0.5-1 µg/day). Syrup Shelcal has 250 mg/5ml of calcium and vitamin D₃ (calcitriol) is available as 0.25 µg capsules. Therapy may be stopped in hypocalcemia secondary to maternal hyperparathyroidism after 6 weeks.

Vitamin D deficiency states: These babies have hypocalcemia associated with hypophosphatemia due to an intact parathormone response on the kidneys. They benefit from vitamin D₃ supplementation in a dose of 30-60 ng/kg/day

Monitoring

The baby is monitored for the Serum calcium, and phosphate, 24 hour urinary calcium, calcium creatinine ratio. Try to keep the calcium in the lower range, as

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defective distal tubular absorption leads to hypercalcemia and nephrocalcinosis.¹⁰

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