REVIEW ARTICLE

Approach to Neonatal Hypocalcemia

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Abstract

Hypocalcemia in neonates is defined as total serum calcium concentration less than 7.5–8 mg/dL and/or ionized calcium less than 4.4 mg/dL in neonates (>1500 g) and total serum calcium concentration less than 7 mg/dL or ionized calcium less than 3.6 mg/dL in low-birth-weight neonates (<1500 g). About 80% of the calcium transfer across the placenta occurs in the last trimester. Parathyroid hormone-related peptide (PTHrP) regulates the positive calcium balance in the placenta. Postpartum serum calcium level in neonates depends on an intricate relationship between PTH and renal and skeletal factors. Based on the timing of the presentation, hypocalcemia can be early onset (develops in the first 72 hours of life) and late onset (occurs after 72 hours of life). Causes of early-onset hypocalcemia include prematurity, SGA, IUGR, birth asphyxia, diabetes mellitus, or toxemia in the mother. Late-onset neonatal hypocalcemia may be caused by increased dietary phosphate content, neonatal vitamin D deficiency, hypomagnesemia, hypoparathyroidism, or parathyroid hormone resistance. We present a neonate with hypocalcemia due to transient hypoparathyroidism secondary to maternal adenoma. A thorough history and physical examination are essential to identify at-risk asymptomatic infants who need screening for hypocalcemia. Neonatal hypocalcemia can be a serious event and can cause serious morbidity and mortality. Majority of the early as well as transient late neonatal hypocalcemia resolves completely, while lifelong treatment may be required in some cases depending on the etiology.

Keywords: Calcium, Hypocalcemia, Neonate.

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Case Presentation

A 14-day-old male infant was brought to the emergency department with the complaints of worsening seizure-like activity since Day 3 of life. He was born at 39 weeks with a birth weight of 3.09 kg via vaginal delivery to a G3 mother and was sent home on Day 2 of life. Mother noticed shaking of his extremities during sleep on Day 3 of life. These episodes gradually increased in severity and frequency. Mother described these events as diffuse generalized stiffening and shaking, facial grimacing, and gaze abnormalities with cyanosis. There were no constitutional symptoms or sick contacts. Current diet included standard neonatal formula.

Maternal history was significant for parathyroid adenoma detected during her second pregnancy. Surgery was deferred as the size of the adenoma reduced after delivery. During her current pregnancy, mother's serum calcium was elevated, with a maximum of up to 12 mg/dL, requiring hydration.

Initial laboratory studies revealed hypocalcemia (serum calcium 5.3 mg/dL), hyperphosphatemia (8.2 mg/dL), hypomagnesemia (1.34 mg/dL), low serum 25 hydroxy vitamin D (25OHD) (12.9 ng/mL), and inappropriately low intact PTH level (19 pg/mL). Other laboratory studies including hematologic, septic, and metabolic workup were normal. The urine calcium creatinine ratio was 0.3 mg/mg.

Introduction and Definition

Hypocalcemia is a common metabolic problem in neonates. Neonatal hypocalcemia is defined as total serum calcium concentration less than 7.5–8 mg/dL and/or ionized calcium less than 4.4 mg/dL in neonates with birth weights more than 1500 g and total serum calcium concentration less than 7 mg/dL or ionized calcium less than 3.6 mg/dL in neonates with birth weights less than 1500 g.[1]

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Neonatal Calcium Homeostasis

Calcium is the most abundant mineral in the human body. About 99% of the body calcium is in bones and only 1% in serum.[2] Approximately half of the serum calcium is in the ionized form at normal protein concentration and is the physiologically active component. Forty percent of calcium is bound to albumin, and 10% is complexed.[3,4]

Factors that regulate calcium homeostasis include parathyroid hormone (PTH), vitamin D, calcitonin, and calcium-sensing receptors (CaSR). The actions of PTH include bone resorption, phosphate excretion, renal calcium, and magnesium reabsorption and increase 1,25 vitamin D (1,25OHD) levels to adult levels by 48 hours of life by increasing the activity of 1-alpha hydroxylase.[5,6] Most importantly, PTH activates the synthesis of calcitriol (1,25OHD) in the renal proximal tubule.[2,4] At higher serum concentrations, calcitriol causes bone resorption and promotes intestinal absorption of calcium and phosphate. Another key hormone for calcium homeostasis, calcitonin, is secreted by the parafollicular cells of thyroid gland and

decreases bone resorption, reduces gastrointestinal absorption of calcium and phosphate, and increases renal calcium and phosphate excretion.[1] PTH regulates calcium by its action on target cells in bone and kidney that express the PTH/PTH-related peptide (PTHrP) or type I PTH receptor.

Calcium regulation in the fetus and the neonate is markedly different from that in the later life. The calcium concentration is higher *in utero* to attain sufficient bone accretion. Transport of bone minerals across the placenta results in higher concentration in the fetus compared to maternal levels. Eighty percent of the calcium transfer across the placenta occurs in the last trimester.[7–9] Active transport is facilitated by transmembrane calcium selective channel TRPV6, calbindin D_{9k}, and plasma membrane calcium-ATPase.[7]

PTH and calcitonin do not cross the placental barrier. PTHrP regulates the calcium balance in the placenta.[4] Serum levels of phosphate, PTHrP, and calcitonin are greater, while 1,25OHD and PTH are lower in the fetus compared to maternal levels. Levels of 25-hydroxyvitamin D_3 (calcidiol) in the fetus approximate that in the mother.[1] After birth, neonates become reliant on the dietary intake of calcium absorbed from the gastrointestinal (GI) tract and skeletal calcium. The parathyroid glands will then respond to the decreased ionized calcium (iCa), although the response generally is insufficient. Serum total and iCa concentrations reach a nadir by 48 hours before increasing to mid-normal range by 72 hours of life. In the newborn, PTHrP and calcitonin levels decrease, and PTH and calcitriol levels increase over the first 48 hours.[1,4,7]

Other factors that influence neonatal calcium levels include magnesium, phosphate, and other anions in the serum, albumin, and pH. Hypomagnesemia can decrease the production of PTH and thus decrease PTH activity[10] or induce resistance to PTH hormone within the renal tubules and in the bone.[11] Serum anions, such as phosphate, citrate, or bicarbonate, increase the concentration of bound calcium and hence decrease the active iCa levels.[3]

Disturbances in acid-base status can influence iCa levels without affecting total calcium levels. In acidosis, H+ ions bind with albumin thereby reducing available albumin to bind with calcium and hence increases iCa levels, while alkalosis decreases the iCa levels.[12,13] Hypoalbuminemia decreases the total calcium levels, while the iCa level remains normal in the absence of other factors that can affect calcium homeostasis.[3,14,15]

Classification of Hypocalcemia

Neonatal hypocalcemia is a potentially life-threatening condition. When determining the etiology of the hypocalcemia, timing of the presentation is important. Hypocalcemia can be classified as early onset when it develops within the first 72 hours of life and late onset after 72 hours of life and usually by the end of first week after birth.[1,16]

Causes of Neonatal Hypocalcemia

Table 1 illustrates the causes of neonatal hypocalcemia.

Table 1: Etiology of neonatal hypocalcemia

Early-onset hypocalcemia[17]
Fetal/neonatal factors
Preterm infants
Low-birth-weight infants
SGA/IUGR babies
Perinatal asphyxia
Hypomagnesemia
Neonatal sepsis
Renal failure
Latrogenic: lipid infusions, citrated blood, bicarbonate
Maternal factors
Maternal diabetes mellitus
Maternal vitamin D deficiency
Toxemia of pregnancy
Maternal hyperparathyroidism
Late-onset hypocalcemia[1,5]
Increased dietary phosphate
Neonatal vitamin D deficiency
Hypomagnesemia
Hyperbilirubinemia and phototherapy
Hypoparathyroidism
Parathyroid hormone resistance

Early-onset Hypocalcemia

Early-onset hypocalcemia results from an exaggerated reduction in serum calcium that physiologically develops within the first 72 hours of life. It is often transient.

Roughly one-third of preterm babies and majority of the very low-birth-weight infants develop early neonatal hypocalcemia.[9,17] The causes of hypocalcemia in premature neonates include premature discontinuation of calcium transfer across the placenta, rapid and more significant fall in serum calcium from intrauterine levels, reduced nutritional intake, delayed secretion of PTH in response to low calcium levels, and decreased target organs response to PTH.[18] Hypocalcemia in low-birth-weight neonates may be secondary to the increased calcium accumulation in bones and resistance to vitamin D action resulting in reduced intestinal calcium absorption and skeletal calcium reabsorption.[9] The mechanism of hypocalcemia in asphyxiation is likely multifactorial, including greater phosphate load secondary to cell death, decreased calcium intake, greater calcitonin secretion, along with concurrent renal failure, and metabolic acidosis.[9,18,19]

Early neonatal hypocalcemia occurs in about half of infants born to mothers with diabetes mellitus. Women with diabetes will have higher serum calcium levels during pregnancy compared to healthy controls.[20,21] Hence, higher serum calcium seen in these babies *in utero* results in suppression of endogenous PTH secretion. Decreased maternal-fetal transfer of magnesium due to increased maternal urinary excretion of magnesium also leads to functional hypoparathyroidism in these neonates.

Late-onset Hypocalcemia

Late-onset neonatal hypocalcemia usually occurs 5–10 days after birth. The etiology is broad.[1,5]

Phosphate content is about seven times greater in cow's milk compared to that in breast milk (956 vs 140 mg/L in breast milk).[9] Infants taking milk formula or evaporated milk with high phosphate load develop hypocalcemia due to poorly soluble calcium salt formation. Increased phosphate will lead to increased PTH secretion or function or may cause increased skeletal deposition of calcium and phosphate causing hypocalcemia.[18,22]

Neonatal vitamin D deficiency may result from vitamin D deficiency in the mother, malabsorption, renal failure, and chronic liver diseases.[23,24] Hypophosphatemia usually accompanies hypocalcemia in these infants.[9]

Magnesium plays an important role in calcium homeostasis.[25] Hypomagnesemia causes PTH resistance and impaired PTH secretion resulting in hypocalcemia.[26] Most hypomagnesemia seen in neonates are transient.[25,27] Defects involving intestinal or renal tubular magnesium transport can result in hypomagnesemia, such as the mutations in the transient receptor melastatin 6 (TRPM6) and CLDN16 genes.[28–30]

Hypocalcemia accompanied by hyperphosphatemia should prompt the evaluation for hypoparathyroidism where PTH level may be low or inappropriately normal.[31] Hypoparathyroidism can be primary or secondary. Primary hypoparathyroidism can be isolated or associated with syndromes such as DiGeorge syndrome.[9] Maternal hyperparathyroidism also may lead to an impairment of the neonatal parathyroid gland's response. Maternal hypercalcemia due to hyperparathyroidism causes increased transfer of calcium. This increased fetal serum calcium suppresses fetal PTH synthesis and stimulates calcitonin secretion.[32]

Isolated causes of hypoparathyroidism include *GMC2*, PTH-gene mutations, autosomal dominant CaSR or *GNA11* mutations, and X-linked *SOX3* mutations.[33,34] Gain-of-function mutations in CaSR reduce the setpoint of CaSR, resulting in no PTH secretion at low calcium levels that would normally trigger PTH secretion.[35,36] These infants have an inappropriately normal-high urinary calcium excretion, in the setting of hypocalcemia due to increased CaSR activity in the kidney.[7]

Syndromic causes of hypoparathyroidism include 22q deletion syndrome, CHARGE association (CHD7), autoimmune polyglandular syndrome type I, and hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome.[34] Mitochondrial cytopathies (Sanjad-Sakati and Kenney-Caffey syndromes) can also lead to hypoparathyroidism.[7,28,34,37] The most common syndromic cause of hypoparathyroidism is DiGeorge syndrome (DGS); the most severe phenotype includes cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia.[7,38,39]

Pseudohypoparathyroidism with end-organ PTH resistance may be transient as seen in babies with renal dysplasia or obstructive uropathy.[40] Permanent pseudohypoparathyroidism is seen in those with GNAS mutations causing pseudohypoparathyroidism type Ia (Albright's hereditary osteodystrophy).[41–43]

Infants with hyperbilirubinemia requiring phototherapy may develop hypocalcemia possibly due to reduced melatonin secretion resulting in increased skeletal uptake of calcium and increased urinary excretion of calcium.[44,45]

Clinical Signs of Hypocalcemia

Many neonates with hypocalcemia are asymptomatic, especially during the initial 72 hours of life. Notable symptoms include neuromuscular hyperexcitability manifested as jitteriness, jerking, tremor, hyperacusis, and focal or generalized seizures.[46] These infants may also exhibit apnea, cyanosis, reduced feeding, tachycardia, and congestive heart failure. Other less common symptoms include inspiratory stridor due to laryngospasm, wheezing due to bronchospasm, or vomiting due to pyloric spasm.[7,9]

Screening: Whom and When

As most infants with hypocalcemia are asymptomatic, serum or preferably ionized calcium should be measured in those at risk for hypocalcemia, such as preterm neonates, infants born SGA/IUGR, infants with a 1-minute APGAR score <4, and infants of diabetic mothers. For babies with extremely low birth weight (birth weight less than 1000 g) or infants with underlying sepsis, ionized calcium should be monitored at 12, 24, and 48 hours of life. For babies with gestational age less than 32 weeks and preterm babies with a birth weight between 1000 and 1500 g, iCal should be checked at 24 and 48 hours of life.[47] Any infant having symptoms consistent with hypocalcemia should be screened.[9] Calcium monitoring should be continued until calcium levels normalize and oral intake is adequate.[47]

Approach to Hypocalcemia in Neonates

A thorough history and physical examination are essential to identify at-risk asymptomatic infants who need screening for hypocalcemia (Tables 2A and B).

Laboratory Workup

Initial laboratory studies include total and iCa and serum phosphorus[9]—see Flowchart 1. As total calcium in serum includes both the free (biologically active) and protein-bound components, iCa should be measured, particularly in the setting of acute illness, premature or ill infants, malnutrition, or hypoalbuminemia. For each unit increase in pH, iCa falls by 0.16 mg/dL. Serum total calcium levels must be corrected for the albumin level (plasma calcium concentration falls by 0.8 mg/dL for every 1.0 g/dL fall in the plasma albumin concentration).

Normal or low phosphate level is seen in vitamin D deficiency, vitamin D resistance, renal loss as in renal tubular defects, and iatrogenic causes, such as administration of citrated blood and bicarbonate therapy. High phosphate concentration may be due to increased phosphate load in the feedings, renal failure, hypoparathyroidism, or pseudohypoparathyroidism.[9] Low PTH can be seen in hypoparathyroidism and hypomagnesemia, while marked or persistent elevation in PTH is seen in vitamin D deficiency and pseudohypoparathyroidism. Serum magnesium level should be checked. Mothers of neonates with low PTH and with normal magnesium should be screened for maternal hypercalcemia and hyperparathyroidism. Infants with primary hypoparathyroidism should undergo detailed genetic and metabolic workup. Urine calcium, magnesium, phosphate, and creatinine levels should be checked in neonates with suspected renal tubular defects.[48]

Imaging studies include chest X-ray to look for absent thymic shadow (in DGS) and status of aortic arch, and echocardiography to evaluate for cardiac truncal defects which can occur in 22q11.2 deletion disorders.[7] Fluorescence *in situ* hybridization (FISH) studies assess for the genetic deletion in 22q11.2. Electrocardiographic (EKG) changes associated with hypocalcemia include a prolonged corrected QT interval, prolonged ST segment, and T-wave abnormalities.

Treatment

Table 3 details the management of hypocalcemia. Asymptomatic infants with hypocalcemia can be managed with oral calcium supplementation. The goal is to ensure adequate calcium intake by initiating early feedings. Formula that provides calcium and phosphorus in 2:1 ratio is optimal. Oral calcium supplements can be given that increases the calcium phosphorus ratio to 4:1 till hypocalcemia is corrected and PTH function is normalized.[9]

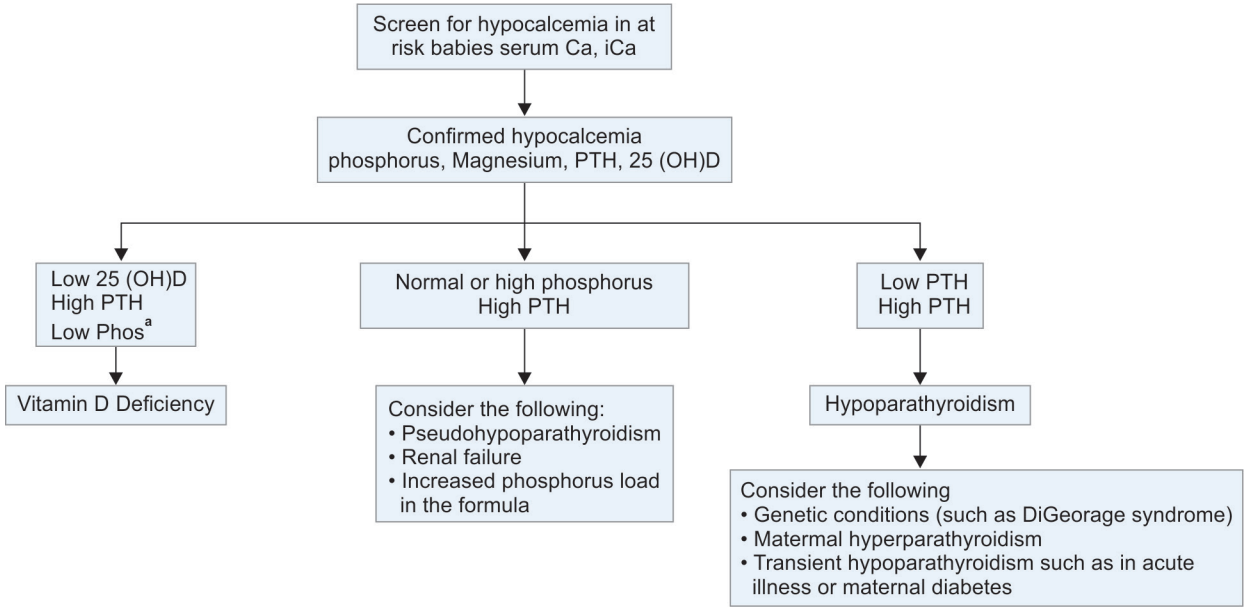
Table 2A: Salient points in the history for neonatal hypocalcemia

History	*Salient points*
Antenatal history	Gestational/permanent forms of diabetes with degree of glycemic control, toxemia of pregnancy, maternal vitamin D deficiency, maternal hyperparathyroidism, maternal medications (excess alkali), and fetal growth restriction
Natal history	Gestational age, birth weight, mode of delivery and associated complications, and perinatal asphyxia
Postnatal history	Day of presentation, feeding method, phosphate content of the formula used, calcium content of the TPN, neonatal sepsis, phototherapy, renal failure, hepatobiliary disease, blood transfusion, and medication review[9]
Family history	DGS, renal calculi, rickets, seizures due to hypocalcemia, and skeletal abnormalities[9]

Table 2B: Key physical examination elements for neonatal hypocalcemia

Vitals: Tachycardia, apnea
Cyanosis, hyperbilirubinemia
Growth parameters: IUGR, SGA
Cardiac failure
Cardiac murmur
Examine for stigmata of 22q11.2 deletion syndrome: Cleft palate, bifid uvula, enophthalmos, ear anomalies, prominent nasal bridge, micrognathia, asymmetric crying facies and craniosynostosis, anteriorly placed or imperforate anus, cardiac defects, infantile hypotonia, congenital talipes equinovarus, polydactyly, cryptorchidism, and hypospadias.[50,51]
Examine for clinical features of Type Ia—Albright's hereditary osteodystrophy: Short fourth, and fifth metacarpals and metatarsals or short fourth metacarpal only "Knuckle, knuckle, dimple, dimple" sign on closed fist.[50,51]

Flowchart 1: Diagnostic evaluation for hypercalcemia[9,50]



For those who are on total parenteral nutrition, 10% calcium gluconate can be added to the solution (50 mg/kg of elemental calcium/day). Treatment is also directed toward other underlying etiologies, such as hypomagnesemia, vitamin D deficiency, and hyperphosphatemia.

Symptomatic infants with tetany/seizures should be managed with 10% calcium gluconate solution 1 mL/kg intravenously over 5–10 minutes with careful monitoring of heart rate and infusion rate. Calcium gluconate at 1 mL/kg can be repeated if no response seen in 10 minutes. Calcium chloride at a dose of 0.2 mL/kg is another preferable alternative. To avoid precipitation of calcium salts, phosphate and bicarbonate should not be infused concomitantly with the calcium. Following the administration of calcium as a bolus, 50–150 mg/kg/day elemental calcium infusion should be initiated until the patient can tolerate oral calcium supplementation.[5]

Once the symptoms are controlled and the patient is able to tolerate supplements by mouth, oral calcium supplementation should commence.[16] Calcium carbonate and calcium citrate have the greatest proportion of elemental calcium (40 and 21% elemental calcium by weight, respectively); they are considered the supplements of choice.

Table 3: Acute management of hypocalcemia

Acute management of hypocalcemia[*5,9]	
Asymptomatic	
Calcium supplementation	Enteral: 50 mg/kg elemental calcium
	TPN: 10% calcium gluconate added to the solution
Symptomatic[α]	
Calcium supplementation	IV calcium gluconate 1 mL/kg over 10 minutes, repeat PRN
	Bolus followed by elemental calcium infusion 50–150 mg/kg/day IV until enteral feeds can be tolerated.
Vitamin D supplementation[β]	
	Vitamin D2/D3 2000 IU daily × 6–12 weeks, then maintenance dose, 400 IU/day
	Calcitriol[£] 0.08–0.1 µg/kg/day

[*]Total calcium <8 mg/dL; iCal <1.2 mmol/L; [α]Seizures or abnormal EKG; [β]Vitamin D2 or 3 in vitamin D deficiency or hypoparathyroidism; [£]Calcitriol short term to correct hypocalcemia in transient or permanent hypoparathyroidism

EKG monitoring is recommended as dysrhythmias can occur if correction is too rapid.[9] Due to potential risk of extravasation of calcium into subcutaneous tissues causing tissue necrosis and calcification of subcutaneous tissues, oral calcium supplementation should be initiated as soon as possible. Other feared adverse effects include hepatic necrosis as a result of infusion via an umbilical venous catheter with tip in a portal vein branch and arterial spasm following intraarterial infusion.[16]

Additional management depends on the underlying etiology. Vitamin D deficiency (low serum 25OHD) is treated by either ergocalciferol (D2) or cholecalciferol (D3). If renal 1 alpha-hydroxylation is impaired, such as hypoparathyroidism or PTH resistance or the vitamin D–dependent rickets syndromes, metabolites that do not require this enzymatic activation should be administered (calcitriol).

For infants with late-onset hypocalcemia, vitamin D3 400 international units/day is given for 1–2 weeks. Calcitriol at a dose of 0.08–0.1 µg/kg can be given to facilitate intestinal calcium absorption and to release calcium from the skeleton.[16] Calcitriol is an active form of vitamin D which has a number of *direct* effects, including (1) increasing intestinal calcium and phosphorus absorption, (2) increasing renal calcium reabsorption, (3) bone resorption and release of calcium, and (4) suppressing parathyroid gland PTH secretion via transcriptional downregulation.[49] Except in cases of hypoparathyroidism, calcitriol is not continued long term.

In hypoparathyroidism, in addition to calcium supplementation and calcitriol, a low phosphate formula is preferred. Those with hyperphosphatemia are given a diet high in calcium and low in phosphorus in addition to oral calcium supplements.[50] Treatment can be further intensified with thiazide diuretics (increasing distal renal tubular calcium reabsorption) and a low salt (dietary sodium restriction). The primary goals of management include symptom control, maintaining serum calcium in the low-normal range, reducing serum phosphorus to a normal range, and maintaining a calcium-phosphate product below 55 mg^2/dL^2. Complications of current therapies for hypoparathyroidism include hypercalciuria, nephrocalcinosis, and soft tissue calcification. Duration of treatment may last from weeks to months in cases of transient hypoparathyroidism and can be permanent in cases of primary hypoparathyroidism.[9]

Follow-up

The neonate in the above case received intravenous (IV) calcium gluconate bolus followed by continuous calcium carbonate (125 mg of elemental calcium/kg/day) via nasogastric (NG) tube as there was no IV access. He also required repletion of magnesium sulfate. Infant was also started on 800 IU vitamin D and 0.05 µg bid calcitriol. His formula was changed to PM 60:40. His further workup showed normal EEG, CT brain, and chest X-ray.

The continuous calcium carbonate supplementation via NG tube was changed to intermittent enteral calcium carbonate as his calcium stabilized over 72 hours. The calcitriol dose was reduced to 0.05 µg once daily. The calcitriol was stopped when the serum calcium reached >9.0 mg/dL. The infant was weaned from calcium supplements by 5 weeks of life and vitamin D by 8 weeks of life. He remained stable and symptom-free with normal serum biochemistries during follow-up.

Conclusion

The patient in the vignette had hypocalcemia, hyperphosphatemia, and inappropriately low intact PTH for the hypocalcemia consistent with hypoparathyroidism. Maternal history of parathyroid adenoma with hypercalcemia suggested transient hypoparathyroidism secondary to chronic maternal hypercalcemia. The concomitant vitamin D deficiency and hypomagnesemia exacerbated the clinical picture. We were able to wean him off all the supplementation by 6–8 weeks confirming a diagnosis of transient hypoparathyroidism. Consideration of the differential for neonates should be kept broad and key history, and physical findings can illuminate the most likely etiology.

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