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Transient Hypercalcemia in Preterm Infants: Insights Into Natural History and Laboratory Evaluation

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Case Presentation

Hospital Course

A premature male infant was born after 31 weeks gestation with birth weight of 1705 g. He was the first baby of nonrelated Ashkenazi Jewish parents. There was no history of inherited, genetic, or metabolic disorders in the whole family except for nephrolithiasis in the mother's family. On admission to the neonatal intensive care unit he was given parenteral nutrition. Enteral feeds were started on day of life (DOL) 2. Parenteral nutrition was discontinued at DOL 7. Full enteral feeds of mother's milk were achieved on DOL 10, when routine vitamin D supplementation of 400 IU/day was started. Cow's milk–based powdered human milk fortifier (Similac, Ross/Abbott-Promedico) was added from DOL 11. Hypercalcemia was first detected on DOL 16 when total calcium levels went up to 13.6 mg/dL (normal range for term newborn levels = 8-11.3) while ionized calcium levels were also high (5.8-5.9 mg/dL on DOL 19-46) with highest levels of 6.07 mg/dL measured on DOL 28. Laboratory evaluation as well as treatment was initiated (Table 1).

Follow-Up

Total serum calcium levels normalized on DOL 64 with 10.5 mg/dL, and urine calcium/creatinine ratio dropped to 1.07 mg/mg only on DOL 72, resolving to normal infant range of 0.5 mg/mg on DOL 87. With oral supplementation phosphorus levels gradually increased up to 6.2 mg/dL on DOL 87. Follow-up renal ultrasound on DOL 80 showed that only one small calculus was left in the lower pole of the left kidney. Routine vitamin D supplementation (400 IU/day) was restarted at DOL 80 because of chemical rickets with rising alkaline phosphatase levels (up to 991 IU/L) despite phosphorus supplementation, $1,25(OH)_2D$ levels dropped to normal range (60 pg/mL) and low 25(OH)D levels (14.9 ng/mL). Alkaline phosphatase levels started to decrease, and hypercalcemia or hypercalciuria did not reappear, suggesting transient infantile hypercalcemia as the most likely diagnosis. Oral phosphate supplementation was discontinued after a month, and the baby maintained normal serum phosphorus levels. At the age of 11 months, the calcium level was 10.1 mg/dLl, phosphorus 6.8 mg/dL, alkaline phosphatase 269 IU/L, parathyroid hormone (PTH) 17 pg/mL, 25(OH)D 41.9 ng/mL, $1,25(OH)_2D$ 60 pg/mL, and urine calcium/creatinine ratio 0.5 (mg/mg). Vitamin D supplementation was discontinued at the age of 18 months. The boy, more than 2 years old, has normalized his serum calcium and phosphorus levels, calcium/creatinine urine ratio, and vitamin D metabolites. On follow-up renal ultrasound the same small calculus (4 mm in diameter) was found in the lower pole of the left kidney without change in its size or any evidence of parenchymal damage, nephrocalcinosis, or renal pelvis dilatation.

Table 2 summarizes data on 5 other asymptomatic preterm infants who presented to us with incidental findings of hypercalcemia and hypercalciuria. Our evaluations of the index case and the other infants led us to consider transient hypercalcemia hypercalciuria as the most probable diagnosis.

Discussion

Calcium and phosphorous are essential minerals that are tightly maintained within their normal ranges by the

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Table 1. Laboratory Evaluation, Imaging Studies, and Treatment of the Index Premature Infant With Hypercalcemia[a].

Laboratory evaluation	*Total protein*: 5.0-5.4 g/dL (4.3-7.6 g/dL); *Albumin*: 3.8-3.9 g/dL (3.2-5 g/dL); *Arterial pH*: 7.33 (7.35-7.45); *Alkaline phosphatase*: initial levels: 425-450 IU/L, 558-616 IU/L on DOL 46-49 and 797-991 IU/L on DOL 64-80; *Phosphorus*: initial levels 6.4-7.0 mg/dL (4.8-8.2 mg/dL), 4.4-4.6 mg/dL on DOL 46-49, and 3.4 mg/dL on DOL 64; *Urine calcium/creatinine ratio*: 5.2 mg/mg (normal for preterm infant 0.80-0.94 mg/mg or 2.3-2.7 mmol/mmol), 6.55 mg/mg on DOL 46; *24-hour urine collection of calcium*: 50 mg/kg/day; *Urine amino and organic acids*: nonspecific mild aminoaciduria; *PTH*: 20.48 pg/mL (15-65 pg/mL) on DOL 30, 9.13 pg/mL on DOL 46; *1,25(OH)2D*: 191 pg/mL (70-100) on DOL 31, 58 pg/mL on DOL 46; *25(OH)D*: 14.90 ng/mL on DOL 46 (deficiency levels 10-20 ng/mL); Thyroid *function tests*: TSH: 5, FT4: 0.95 pmol/L
Imaging studies	Parents laboratory evaluation: *Urine calcium/creatinine ratios for parents*: <0.2 mg/mg (<0.2 mg/mg); *Mother's breast milk content*: protein: 1.5 g/dL; calcium: 42.7 mg/dL or 1.07 mmol/dL; phosphorus 6.8 mg/d or 0.22 mmol/dL
	Renal sonography: 2 small renal calculi in the lower pole of the left kidney without any signs of nephrocalcinosis (on DOL 31); *Chest X-ray*: normal; *Cardiac echo*: normal
Treatment	Intravenous hydration; Routine vitamin D supplementation and human milk fortifier were discontinued; Oral hydration consisted of ad libitum mother's milk (at least 180-200 cc/kg/day); Oral phosphate supplementation (as potassium or sodium salts) on DOL 64

Abbreviations: DOL, day of life; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.
[a]Values in parentheses indicate the normal range.

Table 2. Baseline and Laboratory Data of Premature Infants With Mild Infantile Hypercalcemia.

		Evaluation								
Gestational Age (Weeks)/Gender	Highest Ca Levels	Ionized Ca (mg/dL)	Serum Alb, Phos, ALP	Maximal Urine Ca/Creat Ratio (mg/mg)	PTH Levels (pg/mL)	25(OH)D Levels (ng/mL)	$1,25(OH)_2$ D (pg/mL)	Thyroid Function Tests	Renal Sonography for Suspected Nephrocalcinosis/ Nephrolithiasis	First Normal Serum Calcium Levels
33+4/7; female (sister of first case, born 13 months later)	12.2 mg/dL on DOL 12	6.5 (↑)	Normal	4.3 (↑)	9.1 (↓)	14.9 (↓); at 9 months 21 (N)	103 (↑); at 9 months 76 (N)	Normal	Normal	10.8 mg/dL on DOL 18
33+5/7; female	13.2 mg/dL on DOL 15	6 (↑)	Normal	4.13 (↑)	6.8 (↓)	9.5 (↓)	118 (↑)	Normal	Normal	10.8 mg/dL, on DOL 18
36+4/7; male	13 mg/dL on DOL 10	6 (↑)	Normal	5.7 (↑)	4.4 (↓)	23.4 (↓)	45 (N)	Normal	Normal	10.4 mg/dL on DOL 28
33 weeks; male, twin I	12.3 mg/dL on DOL 15	6.8 (↑)	Normal	2.3 (↑)	12.7 (↓)	14.7 (↓)	—	Normal	Normal	10.8 on DOL 29
33 weeks; male, twin II	11.9 on DOL 15	6.3 (↑)	Normal	2.5 (↑)	9.9 (↓)	19 (↓)	—	Normal	Normal	10.8 on DOL 29

Abbreviations: DOL, day of life; Ion, ionized; Ca, calcium; Alb, albumin; Phos, phosphorus; ALP, Alk Phos, alkaline phosphatase; Creat, creatinine; PTH, parathyroid hormone; ACTH, adrenocorticotropic hormone; N, normal; (↑), high; (↓), low.

combined effect of PTH, calcitonine, fibroblast growth factor 23 (FGF23), and vitamin D metabolites acting on their target organs. Neonates are vulnerable to disorders in calcium levels because of the immaturity of their kidneys, intestines, and parathyroid glands.[1]

There is no well-established normal range for normal calcium serum levels in preterm infants. In term neonates, the upper limit of normal total serum calcium levels is 11.3 mg/dL during the first 3 months of life.[1] Ionized calcium levels of more than 5.4 mg/dL are considered diagnostic for hypercalcemia.[2]

The differential diagnosis of hypercalcemia includes excessive calcium and/or vitamin D supplementation; causes associated with functional hyperparathyroidism (eg, maternal hypocalcemia, congenital parathyroid hyperplasia, inactivating mutations in the Ca^{2+} sensing receptor [eg, familial hypocalcemic hypercalcemia]) or nonparathyroid disease (eg, disorders of vitamin D metabolism, idiopathic infantile hypercalcemia).[1,2] Idiopathic infantile hypercalcemia is a diagnosis of exclusion that may be mediated by vitamin D–dependent mechanism possibly due to 24 hydroxylase excess.[3]

With regard to consequences, hypercalciuria may lead to nephrocalcinosis that might adversely affect the renal function. Most recently, it was reported that nearly 14% of preterm infants had nephrocalcinosis with 57% having spontaneous resolution.[4]

Discussion of the Possible Diagnoses Related to the Combination of Findings Found

Hypercalcemia, Hypercalciuria, and Elevated 1,25(OH)$_2$ Vitamin D$_3$

The most noticed laboratory abnormality was initial elevation of the most active metabolite of vitamin D metabolism, 1,25(OH)$_2$D, a product of hydroxylation of 25(OH)D3 by α-1-hydroxylase normally occurring in the renal tubules and pathologically associated with extra-renal hydroxylation. Moreover, 1,25(OH)$_2$D3 is degraded by 24-hydroxylase.

The differential diagnosis of elevated 1,25(OH)$_2$D accompanied by hypercalcemia and hypercalciuria includes the following: subcutaneous fat necrosis, which was excluded by normal physical examination; granulomatous disease (such as sarcoidosis and tuberculosis) or solid malignancies are extremely rare in infants.[2] Some infants with Williams syndrome have elevated 1,25(OH)$_2$D3 levels, a diagnosis mostly excluded by normal physical examination and normal cardiac echo.[5,6] Elevated levels of 1,25(OH)$_2$D3 in neonatal Bartter syndrome have been reported; however, neither history of polyhydramnios nor hypokalemia or metabolic alkalosis were detected in our baby.[7] A mutation of 24-hydroxylase may also result in decreased degradation of 1,25(OH)$_2$D3.[8] Because of familial history (see also patient 1 [who is the sister of the index case] in Table 2) this possibility was ruled out by genetic analysis that excluded such mutated CYP isoform of the hydroxylase enzyme.

Hypophosphatemia, High 1,25(OH)$_2$ Vitamin D, Hypercalcemia, Hypercalciuria

Intestinal absorption of phosphorus occurs in the small intestine either by a transcellular process, mediated by sodium-phosphate type 2b cotransporter, or by paracellular route, a process that is dependent on the concentration of phosphorus in the intestinal lumen. Renal reabsorption of phosphorus occurs mainly in the proximal tubules. Sodium dependent phosphate cotransporters type IIa and IIc are expressed in the renal proximal tubules and mediate renal phosphate reabsorption.[9] Tubular reabsorption of phosphorus (TRP) is a measure of the capability of the kidney to reabsorb phosphorus, with lower levels indicating phosphate wasting and higher levels indicating phosphate preservation by the kidney.

FGF23 is a humoral factor secreted by the bone. FGF23 reduces renal phosphorus reabsorption by suppressing the expression of renal sodium dependent phosphate cotransporters IIa and IIc and reduces the concentration of 1,25(OH)$_2$D3 by suppressing 25-hydroxyvitamin D-1α-hydroxylase expression. These 2 effects of FGF23 result in reduction of serum phosphorus concentration. Different mutations can lead to low levels of FGF23, causing hyperphosphatemia with high TRP levels and normal to high levels of 1,25(OH)$_2$D3, while other mutations can result in high levels of FGF23 leading to hypophsphatemia, low TRP levels, and low 1,25(OH)$_2$D3.[10] High phosphorus levels exert negative feedback inhibition on the conversion of vitamin D to its active metabolite 1,25(OH)$_2$D3, while hypophosphatemia can lead to compensatory overproduction of 1,25(OH)$_2$D3, which in turn may lead to intestinal hyperabsorption of calcium. This can be caused by mutations in the sodium-inorganic cotransporter, NaPi-IIa, leading to hypophosphatemic rickets with phosphate wasting tubulopathy and high levels of 1,25(OH)$_2$D3 and hypercalcemia. However, in our case phosphorus levels were reduced relatively late (on DOL 46-64) and TRP was all the time very high (99.3% to 99.9%), excluding renal phosphate wasting tubolopathy as a possible cause. Mutations in the FGF23 gene can lead to hyperphosphatemia, enhanced renal phosphate absorption (high TRP), and increased levels of 1,25(OH)$_2$D3 causing tumoral calcinosis.[10] However, in our case, the infant had high levels of 1,25(OH)$_2$D and high TRP, indicating high reabsorption of phosphorus, but normal to low levels of phosphorus that exclude this possibility.

A defect in intestinal phosphorus absorption can also lead to hypophosphatemia, low phosphate in urine (high TRP), and compensatory high levels of 1,25(OH)$_2$D3.[11] However, the rise in serum phosphorus levels after oral phosphate supplementation ruled out this possibility.

Conclusions

The specific cause of infantile hypercalcemia could not be made in slightly higher than two thirds of the cases, leading to the diagnosis of idiopathic infantile hypercalcemia.[6] The cause of this diagnosis of exclusion remains unknown, although it has been associated with an increased intestinal ability to absorb calcium, suggesting the possibility of hypersensitivity to vitamin D.[3]

Hypercalcemia in the neonatal period should be evaluated and treated carefully because of its risks, especially to the kidneys, if associated with hypercalciuria that may lead to nephrocalcinosis. Those with nephrocalcinosis have a much higher calcium levels, than those without it, and as such should undergo wider investigation panel.[6] There is a need for well-established normal ranges for both serum calcium levels and vitamin D metabolites, especially in preterm infants. However, we recommend an individual approach for evaluation of hypercalcemia in these babies, since it appears that many of these cases are transient and seem to resolve spontaneously without any specific treatment. Initial evaluation should thus include blood sampling for total and ionized calcium, pH, albumin, phosphorus, alkaline phosphatase, PTH, as well as spot urine sample for calcium/creatinine ratio in order to assess risk to the kidneys. The addition of $1,25(OH)_2D3$ and calcium-sensing receptor mutation analysis to a panel of investigation may improve the diagnostic yield in infantile mild hypercalcemia.[6] If hypercalciuria is found, renal ultrasonography should be included in the initial evaluation. Calcium intake should be thoroughly reviewed, and whenever high calcium intake related to the use of powdered human milk fortifier or preterm formula is recorded it seems prudent first to stop this extra intake and closely monitor serum calcium levels without immediate further evaluation. It may be judicious also to consider temporarily discontinuing vitamin D supplementation, yet this may carry the risk of provoking or aggravating chemical rickets and osteopenia of prematurity.

Declaration of Conflicting Interests

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References

1. Hsu SC, Levine MA. Perinatal calcium metabolism: physiology and pathophysiology. *Semin Neonatol*. 2004;9: 23-36.
2. Rodd C, Goodyer P. Hypercalcemia of the newborn: etiology, evaluation, and management. *Pediatr Nephrol*. 1999;6:542-547.
3. Nguyen M, Boutignon H, Mallet E, et al. Infantile hypercalcemia and hypercalciuria: new insights into a vitamin D-dependent mechanism and response to ketoconazole treatment. *J Pediatr*. 2010;157:296-302.
4. Mohamed GB, Ibrahiem MA, Abdel Hameed WM. Nephrocalcinosis in pre-term neonates: a study of incidence and risk factors. *Saudi J Kidney Dis Transpl*. 2014;25:326-332.
5. Garabedian M, Jacqz E, Guillozo H, et al. Elevated plasma 1,25-dihydroxyvitamin D concentrations in infants with hypercalcemia and an elfin facies. *N Engl J Med*. 1985;312:948-952.
6. Koltin D, Rachmiel M, Wong BY, Cole DE, Harvey E, Sochett E. Mild infantile hypercalcemia: diagnostic tests and outcomes. *J Pediatr*. 2011;159:215-221.
7. Sharma A, Linshaw MA. A novel compound heterozygous ROMK mutation presenting as late onset Bartter syndrome associated with nephrocalcinosis and elevated 1,25(OH)(2) vitamin D levels. *Clin Exp Nephrol*. 2011;15:572-576.
8. Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med*. 2011;365:410-421.
9. Villa-Bellosta R, Ravera S, Sorribas V, et al. The Na+-Pi cotransporter PiT-2 (SLC20A2) is expressed in the apical membrane of rat renal proximal tubules and regulated by dietary Pi. *Am J Physiol Renal Physiol*. 2009;296:F691-F699.
10. Larsson T, Davis SI, Garringer HJ, et al. Fibroblast growth factor-23 mutants causing familial tumoral calcinosis are differentially processed. *Endocrinology*. 2005;146: 3883-3891.
11. Condon JR, Nassim JR, Rutter A. Defective intestinal phosphate absorption in familial and non-familial hypophosphataemia. *Br Med J*. 1970;18:138-141.