Original Article

Clinical, biochemical, and radiological manifestations of vitamin D deficiency in newborns presented with hypocalcemia

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ABSTRACT

Introduction: The Clinical and radiological manifestations of newborns with severe VDD have not been studied well. **Materials and Methods:** We studied the clinical, biochemical, and radiological manifestations of 10 full-term (FT) newborns (6: M, 4: F) infant presented to with symptomatic hypocalcemia (seizure) secondary to vitamin D deficiency (VDD) during the first 10 days of life are described. All were exclusively breastfed since birth. All their mothers have low 25 hydroxy vitamin D (25OHD) level <10 ng/mL and were not taking vitamin supplements during pregnancy. **Results:** FT newborns with hypocalcemia secondary to VDD presented with generalized convulsions (10/10) and craniotabes (8/10), but none had rachitic chest rosaries or joint broadening. Cranial ultrasonographic evaluation was normal. Serum 25OHD concentrations were low in these newborns (13.2 ± 3.8 ng/mL) and their mothers (8.1 ± 1.5 ng/mL). A total of 60% of them had increased parathormone (PTH) concentrations (>60 ng/mL) and 60% had decreased magnesium (Mg) concentrations (<0.7 mmol/L). Their alkaline phosphatase (ALP) concentrations were significantly higher than normal newborns. All other laboratory results (liver function tests, urea and electrolytes, C reactive protein, lumbar puncture, blood culture, and lactate) were normal. In all patients, seizures ceased within 2 days of starting treatment with alphacalcidol and calcium. Radiological manifestations included metaphyseal band of relative lucency (osteopenia), just under the line of provisional calcification, within distal radius (7/10), femur (4/10), and tibia (3/10), mild cupping and haziness of distal radius (2/10). **Discussion:** Newborns with VDD had significantly lower serum calcium, ALP and PTH and higher phosphate concentrations, compared to older infants with VDD rickets. In newborns with VDD, serum calcium levels were correlated significantly with 25OHD ($r = 0.597$, $P < 0.001$), Mg concentrations ($r = 0.436$, $P < 0.001$) and negatively with ALP concentrations ($r = -0.451$, $P < 0.001$). Serum PTH concentrations were correlated significantly with serum Mg ($r = 0.78$, $P < 0.0001$) but not with serum calcium ($r = -0.103$, $P = 0.3$) or 25OHD ($r = -0.03$, $P = 0.7$) concentrations. **Conclusion:** The clinical, biochemical, and radiological manifestations of VDD in newborns indicate that they are less adapted to VDD compared to older infants. VD supplementation for mothers and newborns should be considered to avoid short-term complications of VDD in the neonatal period and on the growing infants especially in countries with high prevalence of VDD.

Key words: Adaptation, calcium, infants, maternal, newborns, 25OH vitamin D, parathormone, phosphate, radiology, rickets, vitamin D deficiency

Introduction

Recent reports showed high incidence of vitamin D deficiency (VDD) in pregnant women. Placental transfer of 25OHD is the major source of vitamin D to the developing human fetus. There is growing concern about adverse health impacts that VDD during pregnancy may have on the mother, fetus, infant, and later in life.[1-7]

Classically, VDD presents with skeletal manifestations of rickets in childhood and osteomalacia in adults.[3,4,8] However, the clinical and radiological manifestations of severe VDD in newborns are scantily described. Craniotabes in breastfed newborns, with normal serum calcium and phosphorus levels, has been shown to be associated with

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VDD *in utero*, and the deficiency persists at 1 month but becomes undetectable after 3-4 week of treatment with vitamin D.[8,9] Deficient maternal vitamin D status has been shown to be associated with lower birth weight, higher small for gestational age risk and altered neonatal growth, both in weight and in length.[10] Severe VDD deficiency in newborns can also present with hypocalcemia and hypocalcemic symptoms including seizures.[11-13] Rarely, hypocalcemia secondary to VDD deficiency presents as reversible cause of dilated cardiomyopathy in newborns.[14]

The aim of this study was to describe the clinical, biochemical, and radiological manifestations of full-term (FT) newborns with VDD, born to mothers with VDD, who presented with hypocalcemia during the neonatal period.

Materials and Methods

All singleton term infants (gestational age = or >37 weeks, and birth weight >2.5 kg) with VDD and symptomatic hypocalcemia born to VDD mothers. VDD were studied between January 2011 and January 2012. 10 FT infants were identified as candidates for this study who presented with symptomatic neonatal hypocalcemia during the first 10 days of their life (5.9 ± 2.2 days). One hundred FT normal infants, born at the same period, and 18 infants aged >6 months with clinically florid rickets due to VDD served as controls.

Gestational age, measured in weeks completed, was based on maternal dates and early ultrasounds or the modified Ballard score assessment.[15]

All patients were subjected to the following:

- Detailed history taken from the mother including nutritional intake
- Physical examination including clinical manifestations of rickets
- Anthropometric measurements including weight, length, and head circumference. Length was measured with an infant length measuring board: This board has a 100-cm capacity (collapses to 30 cm) and has 0.1 cm increments, with the sliding head-foot piece. The weight was measured using an electronic baby scale with digital display
- Venous blood sample were collected at presentation (5.9 ± 2.2 days of age) for measurement of serum calcium (Ca), phosphate (PO4), albumin, alkaline phosphatase (ALP), parathormone (intact molecule) (PTH), and 25OHD concentrations. The serum was stored at −30°C prior to testing. Serum Ca was corrected for individual variations in serum albumin using the following formula: Corrected serum Ca (in millimoles per liter) = Measured serum Ca (in millimoles per liter) +0.02 × [40 – measured albumin (in grams per liter)]. Newborns and mothers with plasma 25OHD levels less than 10 ng/mL were considered to have VDD. PTH and 25-OH-D were measured by radioimmunometric assay using reagents purchased from Mediagnost (Reutlingen, Germany). Intraassay coefficients of variation were 6.9% and 5.8%, respectively; and interassay coefficient of variations was 8.9% and 8.2%, respectively.

Hypocalcemia was diagnosed when serum calcium <2 mmol/L, hypomagnesemia was diagnosed when serum magnesium <0.7 mmol/L, hypophosphatemia was diagnosed when serum PO4 was <0.9 mmol/L, and high parathormone was diagnosed when PTH (intact molecule) >60 ng/L.[16]

Ethical committee of Hamad Medical Center (HMC) approved the study and informed consent was obtained from all parents of the newborns. For ethical reasons, hormonal concentrations for normal controls were not measured. The presence or absence of radiological evidence of rickets was determined from routine radiographic report of the hand and knee in patients. Informed consents were obtained from the parents.

Statistical analysis

Results were expressed as the mean ± standard deviation. A nonpaired Student's *t* test was used to compare growth parameters and analyte concentrations between hypocalcemic and control groups. Correlation and linear regression analyses were used to investigate the relation between growth parameters and the other variables. Significance was accepted at $P < 0.05$.

Results

Ten FT newborns with hypocalcemia secondary to VDD were recruited in this study. They had gestational age = 37 ± 1.2 weeks compared to normal controls (39.7 ± 1.1 weeks) ($P < 0.05$). Their birth weight, length, head circumference, and the size of anterior fontanel did not differ compared to normal newborns [Table 1].

These newborns with VDD developed neonatal seizure between the 5th and 10th days of their life. Eight out of 10 had craniotabes, but none had rachitic chest rosaries or joint broadening. One newborn had dilated cardiomyopathy diagnosed by chest x ray (CXR) and echocardiography that responded to vitamin D therapy for 4 months.

Table 1: Anthropometric and lab data of newborns with VDD and hypocalcemia

Patients	GA	BWT	L	HC	Ca	Po4	Mg	ALP	Vit D	PTH	Mother Vit D
1	37	2460	48	33	1.87	2.11	0.7	238	15	76	3
2	36	2475	48	33	1.57	2.78	0.74	178	11	90	10
3	36	2460	47	34	1.87	2.23	0.8	261	14	59	10
4	36	3225	52	37	1.45	2.18	0.6	349	7	32	7
5	40	3840	51	36	1.77	2.23	0.6	203	15	23	15
6	36	2822	47	29	1.7	2.06	0.5	226	16	8	12
7	37	3585	54	36	1.4	2.22	0.56	247	12	33	4
8	37	3202	51	35.5	1.7	2	0.7	223	22	66	4
9	38	2190	46	31	1.47	1.9	0.65	235	10	67	8
10	36	1950	46	29	1.6	2.35	0.61	346	10	66	9
Mean	36.9	2820.9	49	33.35	1.64	2.206	0.646	250.6	13.2	52	8.2
SD	1.16385	561.459	2.52262	2.62895	0.15345	0.21718	0.08126	50.6417	3.78514	23.7869	3.45884899

BWT: Birth weight, GA: Gestational age, HC: Head circumference, L: Birth length, PTH: Parathormone, VDD: Vitamin D deficiency, SD: Standard deviation

Neurological examination was within normal limits. Cranial ultrasonography was normal in all patients.

Hypocalcemic newborns had serum 25OHD concentrations = 13.2 ± 3.8 ng/mL and their mothers had 25OHD concentrations =8.1 ± 1.5 ng/mL. Serum magnesium was low (0.65 ± 0.08 nmol/L) in all. Their serum ALP concentrations were significantly higher than normal newborns. A total of 6/10 patients had increased PTH concentrations (>60 ng/mL). Serum PO4 concentration did not differ between patients and normal newborns [Table 2].

Newborns with VDD had significantly lower serum calcium, ALP and PTH and higher PO4 concentrations compared to older infants with VDD [Table 3].

In newborns with VDD, plain x-ray studies performed between the 5th and 10th days after birth showed a metaphyseal band of relative lucency (osteopenia) (8/10), just under the line of provisional calcification, within distal radius (7/10), femur (4/10) and tibia (3/10) [Figure 1]. Mild cupping and haziness of distal radius and ulna occurred in two patients [Figure 2]. No significant change was seen in the cortical thickness or trabeculations of the other long bones.

In newborns with VDD, serum calcium levels were correlated significantly with 25OHD concentrations ($r = 0.597$, $P < 0.001$), magnesium concentrations ($r = 0.436$, $P < 0.001$), and negatively with ALP concentrations ($r = -0.451$, $P < 0.001$). PTH concentrations were correlated significantly with serum magnesium ($r = 0.78$, $P < 0.0001$) [Figure 3] but not with serum calcium ($r = -0.103$, $P = 0.3$) or 25OHD ($r = -0.03$, $P = 0.7$) concentrations.

All newborn patient with VDD were started on alphacalcidol (100 ng/kg once a day, which was reduced to 50 ng/kg/day after 1 week), and calcium supplements (0.25 mmol/kg/day). In all patients, seizures ceased within 2 days of starting treatment.

Table 2: Anthropometric and biochemical data of newborns with Vitamin D deficiency versus controls

	Controls (*n*=40)	Patients (10)
Gestational age (week)	39.7±1.1*	36.9±1.16*
Length (cm)	50.2±3.5	49±2.5
Weight (g)	3051±597	2820±561
HC (cm)	34.7±1.5	33.35±2.6
Calcium (mmol/L)	2.31±0.16*	1.64±0.15*
Phosphate	2±0.17	2.2±0.12
Alkaline phosphatase (IU/L)	165±52	251±51*

*$P<0.05$ patients versus controls, VDD: Vitamin D deficiency, HC: Head circumference

Table 3: Anthropometric and lab data of newborns versus infants with Vitamin D deficiency

	Newborns with VDD (*n*=10)	Infants with VDD (*n*=18)
Age (weeks)	1.5±0.39	67.5±25*
Length SDS	−0.63±0.3	−1.4±0.4
25OHD (ng/mL)	6.5±2.8	8.8±1
PTH (pg/mL)	69±25	237±98*
Calcium (mmol/L)	1.64±0.15	2.03±0.18*
Phosphate (mmol/L)	2.2±0.12	1.25±0.21*
Alkaline phosphatase (IU/L)	251±51	1225±365*

*$P<0.05$ infants versus newborns, PTH: Parathormone, VDD: Vitamin D deficiency, LSDS: Length standard deviation score

Discussion

VDD during pregnancy has been associated with neonatal hypocalcemia, osteopenia, hypoplasia of the enamel of primary teeth, slow statural growth during the 1st year of life and uncommonly with neonatal rickets.[17-24]

Rickets is a bone disease caused by a deficiency of vitamin D that causes decreased calcium absorption from the intestine and abnormalities in formation and mineralization of skeletal bone and results in weak bones, along with slowed

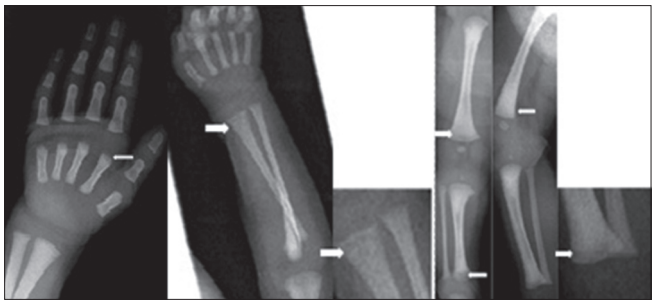

Figure 1: Metaphyseal band of relative lucency (just under the line of professional ossification) within distal radius, femur, and tibia

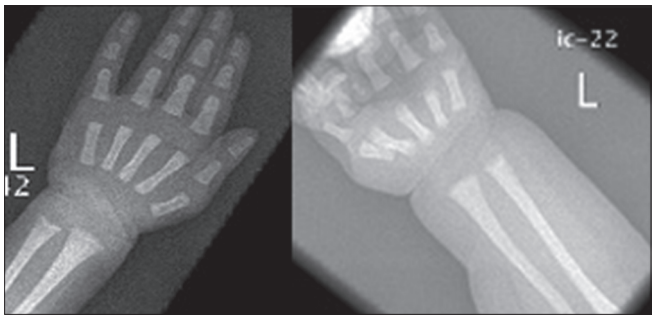

Figure 2: Mild cupping and haziness of distal radius and ulna

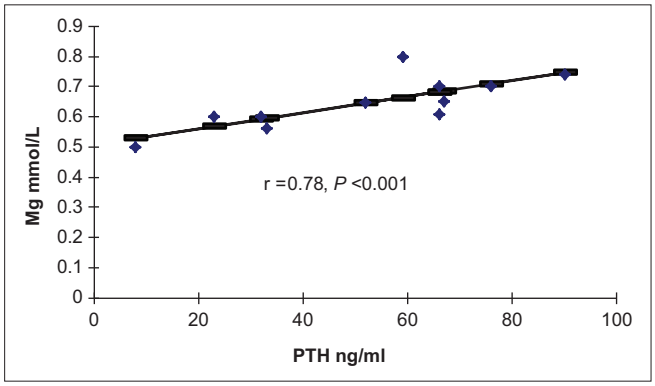

Figure 3: Correlation between parathormone and Mg concentrations in newborns with vitamin D deficiency

growth and skeletal development.[17,18,25] Although there have been sporadic case reports of congenital rickets, the characteristics of early-onset rickets are not well-described. Here, we report our experience with 10 newborns presenting with hypocalcemia due to VDD in the first 2 weeks of life and characterize their clinical, biochemical, and radiological features in comparison with older infants (>6 months) with VDD rickets.

Observational studies and clinical trials found a relationship between maternal vitamin D status and neonatal calcium metabolism, with a greater risk of hypocalcemia among infants born to vitamin D deficient mothers.[26] Our newborns with VDD, born to VVD mothers, who presented with symptomatic hypocalcemia had normal serum phosphate, mild or no elevation (60%) of PTH level levels in response to hypocalcemia and mild increase of ALP level. Clinically, 80% of them had craniotabes and 80% had radiological changes. Hatun *et al*.,[27] reported symptomatic hypocalcemia (79%), normal or high serum phosphate concentrations (71%) and subtle radiological changes in their young infants with VDD during the first 3 months of life.

These biochemical, hormonal, and radiological manifestations of neonatal rickets differed significantly from those for older infants with VDD. Older infants with VDD rickets had normal serum calcium, low serum phosphorus, markedly elevated serum alkaline phosphatase, low 25OHD levels, and secondary hyperparathyroidism that enabled them of better adaptation compared to newborns with VDD.[28,29]

Vitamin D and 25OHD cross the placenta during the last months of gestation and establish vitamin D stores for the newborn. Cord concentrations of the major vitamin D metabolites are consistently lower than those measured in the mother's serum. Placental vein 25OHD correlates significantly with those found in the maternal circulation, implying that it diffuses easily across the placental barrier and that the vitamin D pool of the fetus depends entirely on that of the mother. After birth, vitamin D requirements of infants are influenced by the body stores at birth, which in turn are related to the length of gestation and maternal stores.[30-32] Breastfed infants rely primarily on cutaneous synthesis to maintain a normal vitamin D status because the amount of vitamin D obtained through human milk is usually insufficient (12-60 U/L).[33,34]

Abruptly severed from the placental supply of nutrients after birth, newborns must adapt rapidly to ensure positive calcium balance for normal skeletal growth and development. In healthy, FT newborns, total and ionized calcium concentrations progressively decrease after birth, so that by the 2nd or 3rd day of life calcium concentrations are often lower than that those found in older infants and children. Serum PTH concentrations tend to be low in cord blood but increase within the first 48 h of life in response to the decrease in serum calcium. The latter also induces increased synthesis of 1,25-dihydroxyvitamin D to the 5th day of life in a normal fashion. The mainly passive absorption of intestinal calcium during the first 4-5 days after birth changes to the active 1-25 dihydroxyvitamin D dependent mechanism and therefore calcium concentrations usually return to normal by 5-10 day of age.[35] This explains the occurrence of hypocalcemia in our newborns with low 25OH D because of lack/or attenuation of these changes (adaptation).[36-39] The significant correlation between serum calcium and 25OHD concentrations in our newborns with VDD supports this view.

In addition, in our VDD newborns, the low calcium and 25OHD levels were not associated with adequate increase PTH level (as occurred in older infants with VDD), denoting relative deficiency of PTH secretion in response to hypocalcemia. PTH concentrations were not correlated with serum calcium or 25OHD levels. The significant correlation between serum magnesium and PTH concentrations in our VDD newborns supported this explanation. In accordance with our findings, most patients with Mg deficiency and hypocalcemia have low or inappropriate normal (for the hypocalcemia) serum concentrations of PTH. Serum concentration of 1,25(OH)2-vitamin D is usually low in hypocalcemic Mg deficient patients. Hypomagnesemia can impair PTH secretion and induce resistance to PTH. Both lead to decreased renal synthesis of 1,25(OH)2-vitamin D. Magnesium deficiency induces skeletal resistance to the action of PTH.[40-44]

Similarly, Thomas *et al*.,[8] studied 78 infants moderate-to-severe transient neonatal hypocalcemia at median age of 8.0 days. Their neonates were severely hypocalcemic and hyperphosphatemic. Seventy-five of 78 were hypomagnesemic, and the majority had low or inappropriately normal parathyroid hormone responses. Levels of 25-hydroxyvitamin D were ≤25 ng/mL. All infants responded to therapy of limited duration with 1 or more of the following: Calcium supplements, calcitriol, low phosphorus formula, and magnesium supplementation. They suggested that severe late-onset neonatal hypocalcemia is often a sign of coexistent vitamin D insufficiency or deficiency and hypomagnesemia, and is readily managed with therapy of limited duration.

Other possible explanation is that maternal VDD leads to secondary hyperparathyroidism, which results in a transitory hypoparathyroidism and hypocalcemia in the neonate.[45] A controlled study showed that maternal vitamin D supplementation dampens the decrease in serum calcium observed in newborns at 4 day of age.[39] Maternal vitamin D supplementation may allow ready transfer of a large pool of 25-hydroxyvitamin D to the newborn followed by rapid renal synthesis of 1,25-dihydroxyvitamin D to meet the needs of the newborn: This view is supported by the higher values of circulating 1,25-dihydroxyvitamin D observed at 4 day of age in infants born to supplemented mothers.[46]

Ahmed *et al*.,[47] reported 65 infants with neonatal hypocalcaemic seizures, who were totally breast fed and did not receive vitamin D supplementation, and subsequently found to have rickets. In a subgroup of 15 mothers and their infants, had very low plasma levels of 25(OH) vitamin D.

The normal serum phosphate concentration in our newborns may be explained also by the relative renal immaturity of phosphate handling and/or resistance to the phosphaturic effect of PTH levels in these newborns compared to those in older infants. Low serum calcium concentrations, even in the presence of normal PO4 concentrations, (low calcium × phosphate solubility product) may explain in part the defective mineralization of the metaphysis that appeared in 8/10 of these patients.

Data relating to vitamin D and fetal bone growth are limited. A study of 198 children born in the United Kingdom indicated that the maternal use of vitamin D supplements was significantly associated with greater childhood bone mineral mass and vitamin D supplementation of pregnant women can decrease bone resorption in vitamin D inadequate newborns.[6,20,48] In this study, 8/10 of our hypocalcemic newborns with VDD had craniotabes and radiological evidence of bone disease in the metaphysis (metaphyseal band of osteopenia) of long bones. It is known that osteoporosis of any etiology developing *in utero*, or during infancy, is most pronounced in the metaphyses and may assume a striped appearance that we found in our newborns with VDD.[9] Craniotabes in FT newborn is a further evidence of bone affection by VDD *in utero*.[10] Other studies showed that maternal vitamin D status can affect bone mineral accrual during the intrauterine period and influence bone size at birth.[6,49-51] Collectively, these data provide evidence that *in utero* VDD is important for bone development and growth. It appears that newborns, especially those with VDD due to maternal VDD, are less adapted than older infants and toddlers to VDD because they have lower PTH secretion in response to hypocalcemia, decreased skeletal response to PTH, and decreased bone mass.[28,51]

In conclusion, hypocalcaemia in newborns with VDD is exaggerated by the relatively immature PTH response to hypocalcemia. In countries with high prevalence of VDD, maternal vitamin D supplementation during pregnancy and early supplementation of vitamin D to newborns should be considered to avoid hypocalcemia and skeletal abnormalities in the newborns and growing infants.

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