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## Case Report

# Vitamin D deficiency associated with dilated cardiomyopathy in early infancy caused by maternal cholestasis

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**Abstract.** Breast feeding is known to be a major cause of vitamin D deficiency in infants because the content of vitamin D in breast milk is significantly lower than that in formula. We report a case of a 1-mo-old boy who developed hypocalcemic seizures and dilated cardiomyopathy caused by vitamin D deficiency despite being fed a sufficient amount of regular formula. The cause of vitamin D deficiency in this case was maternal vitamin deficiency due to severe hyperemesis and insufficient sunlight exposure, induced mainly by the malabsorption of fat-soluble vitamins caused by maternal cholestasis. We should carefully consider maternal conditions during pregnancy and the postpartum period to detect and prevent vitamin D deficiency in the fetus and infant.

**Key words:** vitamin D deficiency, hypocalcemia, formula, dilated cardiomyopathy, cholestasis

## Introduction

Vitamin D deficiency during pregnancy is sometimes observed and is mainly attributed to decreased maternal intake of vitamin-D-containing foods and skin protection from sunlight (1). Consequently, low vitamin D levels are sometimes detected in the blood of pregnant women and in newborn cord blood as well. Critical consequences of vitamin D deficiency in early infancy are rare when babies are fed a formula containing vitamins. The content of vitamin D in formula ranges from 6.5 to 9.3 μg in 100 g, which is 20 times more than that in breast milk (0.3 μg in 100 g) (2). Although the vitamin D content in formula in Japan is lower than that recommended by Western guidelines, severe phenotypes of vitamin D deficiency rarely develop in infants fed with regular formula.

We herein report a 1-mo-old boy who developed severe vitamin D deficiency, complicated by hypocalcemic seizures and dilated cardiomyopathy, despite self-demand feeding with Japanese regular formula. Extensive medical history-taking revealed that maternal cholestasis during pregnancy played a critical role in the development of severe vitamin D deficiency in the fetus and subsequent clinical symptoms in infancy.

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**Table 1** Laboratory data on admission at 48 days of age

| | | | | | |
|---|---|---|---|---|---|
| WBC | 9230 /μl | TP | 5.2 g/dl | TSH | 0.412 μIU/ml |
| RBC | 233 $10^3$/μl | Alb | 3.63 g/dl | FT3 | 3.1 pg/ml |
| Hb | 7.4 g/dl | T-Bil | 3.81 mg/dl | FT4 | 1.02 ng/dl |
| Ht | 22.1 % | AST | 53 IU/L | intact PTH | 306 pg/ml |
| MCV | 94.8 $\mu m^3$ | ALT | 27.4 IU/L | 25(OH)Vit$D_2$ | <4.0 ng/ml |
| MCHC | 33.5 % | ALP | 2137 IU/L | 25(OH)Vit$D_3$ | <4.0 ng/ml |
| PLT | 37.8 $10^3$/μl | BUN | 9.2 g/dl | | |
| | | Cr | 0.16 mg/dl | | |
| | | UA | 4.62 mg/dl | | |
| | | Na | 137.4 mEq/L | | |
| | | K | 4.2 mEq/L | | |
| | | Cl | 106.1 mEq/L | | |
| | | Ca | 6.13 mg/dl | | |
| | | P | 7.29 mg/dl | | |
| | | Mg | 1.8 mg/dl | | |

## Case Report

A Japanese boy was born at 37 wk 4 d of gestation by caesarean section. The neonate was born without asphyxia but with a low birth weight (1,830 g) and was admitted to the neonatal intensive-care unit. He was managed with regular formula and had appropriate weight gain. Hypocalcemia was not detected during admission, and he was discharged at 24 d of age. The laboratory and echocardiogram data at discharge were as follows: serum calcium, 9.2 mg/dl; ionized calcium, 2.57 mEq/l, and normal wall motion with a left ventricular ejection fraction of 78%. After discharge, he consumed regular formula well, and had appropriate weight gain. However, he did not receive enough sunlight at home for about 1 mo.

At 48 d of age, he developed an afebrile seizure and was transferred to the pediatric clinic of the regional emergency center. The blood test revealed hypocalcemia (Ca 5.5 mg/dl), and he was then transferred to our hospital. At the time of admission, he had intermittent convulsions and continuous irritability. His measurements were as follows: height, 48.0 cm (–2.18 standard deviations [SD]); weight, 3,700 g (Kaup index 16.1); and head circumference, 38.0 cm (–0.71 SD). His body temperature was 36.5°C, with blood pressure 98/64 mmHg, heart rate 156/min, and percutaneous oxygen saturation 99%. Laboratory findings demonstrated hypocalcemia (Ca 6.13 mg/dl), and high levels of alkaline phosphatase (ALP) and intact PTH (ALP, 2,137 IU/l; intact PTH, 306 pg/ml). Further evaluation revealed severe hypovitaminosis D, below the detection levels of serum vitamin D2 and D3 (Table 1). Chest X-ray revealed no pulmonary congestion or cardiomegaly, with a cardiothoracic ratio of 52% (Fig. 1a). Wrist X-ray showed no signs of rickets. Intravenous administration of calcium gluconate at 5 ml/kg/d followed by oral calcium supplementation at 35 mg/kg/d and alfacalcidol at 0.15 μg/kg/d soon stabilized his hypocalcemia. Serum intact PTH and phosphorus levels were normalized in a few months (Fig. 2).

After taking an intensive family medical history, we noted important information about his mother. At 36 yr of age, she developed hyperemesis during early pregnancy and stayed in bed most of the day without adequate intake of food, resulting in severe weight loss. During late pregnancy, she developed hypertension, and received oral methyldopa starting at 35 wk of gestation. Two weeks later, at 36 wk and 6 d of gestation, jaundice appeared, and a blood test detected the presence of cholestasis with marked elevation of serum bilirubin and leucine

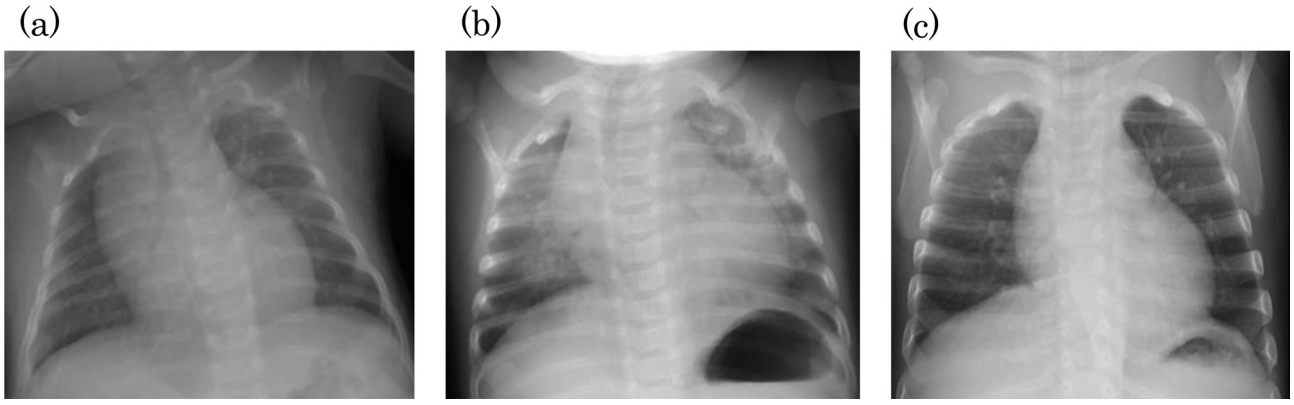


**Fig. 1.** Chest X-ray. (a) At hospitalization (48 d of age). (b) At 17 d of hospitalization (65 d of age): Cardiomegaly (cardiothoracic ratio 66%) and pulmonary congestion were observed. (c) At 170 d of age. The cardiothoracic ratio was almost normal (56%), and the permeability of both lung fields was normalized.

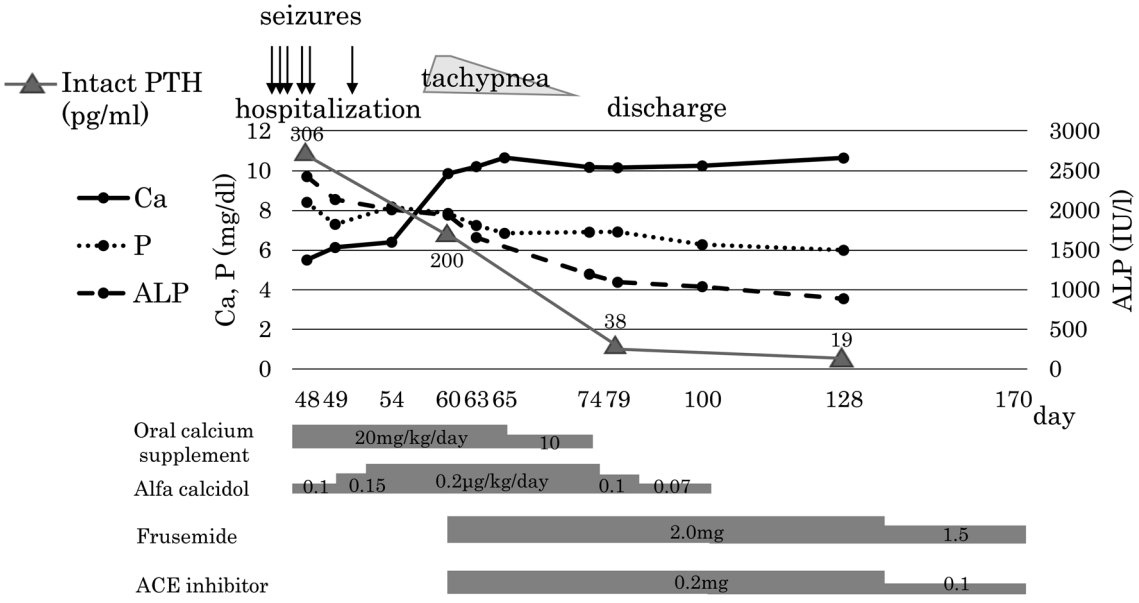


**Fig. 2.** Clinical course of the infant. Convulsions manifested several times during the first week of admission. At about 60 d of age, tachypnea gradually appeared, and dilated cardiomyopathy was diagnosed; a diuretic and an angiotensin-converting enzyme inhibitor were started. The acute heart failure was stabilized within about 2 wk (74 d of age).

aminopeptidase (LAP; 632 U/l). The total and direct bilirubin levels were 8.37 mg/dl and 5.69 mg/dl, respectively. Drug-induced cholestasis was suspected, and methyldopa treatment was discontinued. The jaundice and liver dysfunction (with peak aspartate transaminase [AST] and alanine transaminase [ALT] levels of 108.0 IU/l and 119.5 IU/l, respectively) spontaneously recovered. During this event, fetal growth retardation was observed, and caesarean section was carried out at 37 wk 4 d of gestation.

Intensive treatment of hypocalcemia due to vitamin D deficiency successfully stabilized his clinical and biological condition. However, at 12 d of hospitalization (60 d of age), tachypnea gradually appeared, and echocardiography revealed

depressed LV function with a dilated LV. Chest radiography showed apparent cardiomegaly with a cardiothoracic ratio at 66% and the presence of a butterfly shadow in the lung fields (Fig. 1b). The level of N-terminal prohormone of brain natriuretic peptide was markedly high (3,242 pg/ml). He was diagnosed with congestive heart failure due to dilated cardiomyopathy. Treatment with furosemide and an angiotensin-converting enzyme inhibitor was immediately started, and the cardiac condition gradually improved after 1 wk. At 26 d of hospitalization, oral calcium was discontinued, and he was discharged at day 30 of hospitalization. Alfacalcidol was discontinued at 100 d of age. At 170 d of age, cardiac function had recovered to almost normal, with normal findings of wall motion on echocardiography and a cardiothoracic ratio of 56% without congestion in the lung fields on chest X-ray (Fig. 1c). Diuretic therapy was discontinued at this time (Fig. 2). The laboratory data of the mother (at 72 d of age for her infant) showed improvement in cholestasis, but hypovitaminosis D was still observed: 25(OH)D2, < 4.0 ng/ml; 25(OH)D3, 14.0 ng/ml.

## Discussion

The present case demonstrated several key findings of vitamin D deficiency in infants. First, cholestasis in the mother during late pregnancy was able to cause severe malabsorption of lipophilic vitamins and typical clinical symptoms of vitamin D deficiency in her infant as late as 1 mo of age, even when the infant was fed a regular formula. Second, dilated cardiomyopathy appeared gradually, even after starting calcium and vitamin D supplementation, and recovered within several months of supplementation with medical treatment for heart failure.

A review of cases of infants with vitamin D deficiency showed that this condition occurred mostly in breast-fed infants of mothers with or without vitamin D deficiency during pregnancy and lactation periods. The onset of an afebrile seizure with hypocalcemia due to vitamin D deficiency seems rare for formula-fed infants; however, cases of maternal hyperparathyroidism, distinct restriction of sunlight exposure, severe hyperemesis during pregnancy, and twin or multiple pregnancy were reported causes (3–5).

In the present case, the combination of insufficient intake due to pregnancy hyperemesis, lack of sunlight exposure in both the mother and infant and —probably the major cause— drug-induced cholestasis causing malabsorption of fat-soluble vitamins induced severe vitamin D deficiency in the baby during the fetal and neonatal periods. Our findings indicate that carefully taking a prenatal maternal medical history and noting issues such as hyperemesis, a lack of sunlight exposure, any history of jaundice, and postnatal factors, including breast milk or formula nutrition and restriction of sunlight exposure, is important for the early detection of vitamin D deficiency and early supplementation. In addition, this case showed that clinical manifestations of seizure due to hypocalcemia could occur as late as 1 mo of age, even with persistent vitamin D deficiency in the fetal and neonatal periods.

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus with an onset in the second or third trimester of pregnancy or elevated serum aminotransferases and bile acid levels, and by the spontaneous relief of signs and symptoms within several weeks after delivery (6). ICP is observed in 0.1–1.5% of pregnancies in most areas of Central and Western Europe and North America but is rarely found in Asian countries, including Japan (7). Cases of drug-induced cholestasis, in contrast, may increase in number as new drugs are developed and used. Drug-induced cholestasis is clinically difficult to distinguish from ICP in pregnant women under medical treatment. Cholestasis typically causes malabsorption of lipids, often resulting in lipid-soluble vitamin deficiencies, and can cause a critical phenotype in the fetus and infant. Although whether the present case

had drug-induced cholestasis due to methyldopa or just ICP was unclear, underlying lipid-soluble vitamin deficiencies in pregnant women with cholestasis should be carefully considered, and the presence of a vitamin D deficiency should be monitored in cholestasis-affected women as well as their babies.

The first clinical examination is especially important for the differential diagnosis of hyperphosphatemic hypocalcemia, which is an unusual manifestation of vitamin D deficiency. Meanwhile, previous reports had shown that serum phosphorous levels could increase in severe vitamin D deficiency, presumably due to resistance to the phosphaturic effects of PTH from autologous desensitization of the PTH receptor or insensitivity to PTH-induced signal transduction in renal tubular cells. Although we did not evaluate the percentage of tubular reabsorption of phosphate and urinary calcium excretion rate at the first presentation in this case, laboratory data for the differential diagnosis of pseudohypoparathyroidism would be clinically important for infants with hyperphosphatemic hypocalcemia (8, 9).

Previous reports have shown that dilated cardiomyopathy can be accompanied by hypocalcemia due to vitamin D deficiency. Hypocalcemia caused by hypoparathyroidism, such as DiGeorge syndrome, is also accompanied by cardiomyopathy in some cases (10). In a review of 59 cases with dilated cardiomyopathy due to hypocalcemia, most cases showed a reversible course with a good prognosis using treatment with calcium preparations (11). Cardiac function normalized after a range of periods: 12.4 mo on average (12), 8 to 12 wk (13), or 2 to 5 mo (median, 3 mo) (14). On the other hand, 5 deaths were reported (11). To our knowledge, detailed clinical data on the course of cardiomyopathy associated with hypocalcemia have rarely been reported, suggesting that dilated cardiomyopathy gradually develops despite normalization of calcium concentration in the blood with vitamin D supplementation, and that cardiac dysfunction gradually improves over several months. Further studies with more patients are needed to clarify whether this clinical course was specific to this patient or typical of cardiomyopathy induced by severe vitamin D deficiency.

In conclusion, maternal cholestasis should be considered a risk factor for lipid-soluble vitamin deficiencies, especially vitamin D deficiency. Dilated cardiomyopathy due to vitamin D deficiency may clinically appear, even after the successful treatment of calcium metabolism.

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