

Original Article

A Spectrum of Clinical Presentations in Seven Japanese Patients with Vitamin D Deficiency

Takuo Kubota¹, Tomoo Kotani², Yoko Miyoshi¹, Yoko Santo¹, Haruhiko Hirai¹, Noriyuki Namba^{1, 4}, Masaaki Shima³, Kazuo Shimizu², Shigeo Nakajima¹ and Keiichi Ozono¹

¹Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan

²Department of Pediatrics, Toyonaka Municipal Hospital, Osaka, Japan

³Department of Pediatrics, NTT West Osaka Hospital, Osaka, Japan

⁴The First Department of Oral and Maxillofacial Surgery, Osaka University Graduate School of Dentistry, Osaka, Japan

Abstract. Recently, the reemergence of vitamin D deficiency in developed countries has been pointed out. Vitamin D deficiency is diagnosed based on the serum 25-hydroxyvitamin D (25OHD) level. However, its normal range is still controversial, making the diagnosis of vitamin D deficiency difficult. Here, we present seven Japanese patients diagnosed with vitamin D deficiency. Three patients complained of leg bowing, and the other four of tetany. The patients with leg bowing were toddlers. Radiographic surveys demonstrated evidence of rickets. Laboratory findings showed decreased levels of serum inorganic phosphorus and increased levels of alkaline phosphatase (ALP) and intact-parathyroid hormone (iPTH). The serum levels of 25OHD were relatively low, ranging from 13 to 15.2 ng/ml. Of the patients with tetany, three were young infants. Laboratory findings showed decreased levels of serum calcium and increased levels of ALP and iPTH. The serum levels of 25OHD were markedly decreased (below 8 ng/ml). Thus, these results indicate that relatively low levels of 25OHD can cause rickets, a symptom of vitamin D deficiency, and that clinicians should therefore carefully evaluate the levels of 25OHD.

Key words: Vitamin D deficiency, 25-hydroxyvitamin D, rickets, hypocalcemia

Introduction

Vitamin D deficiency has been increasingly reported in recent years, particularly among children (1, 2). Diet and sunlight exposure are the main determinants of vitamin D levels, and

thus inadequate vitamin D acquisition through either poor dietary intake or limited sunlight exposure leads to depletion of vitamin D stores. This condition results in lowered calcium availability and secondary hyperparathyroidism, often accompanying renal phosphate losses, contributing to tetany and rickets. It is well known that an extremely imbalanced diet causes vitamin D deficiency. In addition, it has been thought that infants who are breast-fed but do not receive supplemental vitamin D or adequate sunlight exposure are at increased risk of

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Correspondence: Dr. Keiichi Ozono, Department of Pediatrics, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan
E-mail: keioz@ped.med.osaka-u.ac.jp

developing vitamin D deficiency (3, 4). Hence, in 2003, the Committee on Nutrition of the American Academy of Pediatrics recommended 200 IU/day vitamin D for all infants and children who were ingesting less than 500 ml/day of vitamin D-fortified formula or milk. Moreover, maternal vitamin D status during pregnancy has been shown to affect neonatal calcium homeostasis (5, 6). It has been considered that adequate vitamin D concentrations during pregnancy are necessary to respond to the calcium demands of the fetus and neonatal handling of calcium.

Circulating 25-hydroxyvitamin D (25OHD) levels are the best clinical indicators of cutaneous synthesis and oral ingestion of dietary sources of vitamin D. Although various commercial laboratories provide the 25OHD assay, the lower limit of 25OHD can vary from 8 ng/ml to 15 ng/ml or even 20 ng/ml (7). The variability makes it difficult for clinicians to diagnose patients with vitamin D deficiency.

We report the clinical presentations of seven Japanese patients with vitamin D deficiency with tetany and rickets, and discuss the clinical manifestations of vitamin D deficiency and 25OHD levels that cause vitamin D deficiency.

Subjects and Methods

The seven Japanese patients were referred to four hospitals, Osaka University Hospital, Toyonaka Municipal Hospital, Osaka Kouseinenkin Hospital, and Hyogo Prefectural Nishinomiya Hospital, in the Kansai region between 1996 and 2004. We asked the patients and their parents about their chief complaints, histories of present illness, birth, family, diets, and frequency of going outside. We made physical examinations and took blood and urine samples. Serum calcium, inorganic phosphorus, creatinine, alkaline phosphatase (ALP), 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), and intact-parathyroid hormone (iPTH), and urine

calcium, inorganic phosphorus, and creatinine, were measured. Serum 25OHD was measured by a competitive protein-binding assay (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan) and the reference range was 9.0–33.9 ng/ml. The patients' clinical findings were all consistent with vitamin D deficiency. They had no liver, renal, or parathyroid disease, fat malabsorption, magnesium deficiency, or anticonvulsant-associated rickets.

Results

Of the seven Japanese patients, three complained of leg bowing, and the other four of tetany. These two groups had characteristic clinical features (Tables 1, 2). The patients with rickets were 17 to 29 mo old. All had been breast-fed and not bottle-fed. Two patients did not have restricted diets, and one patient had a restricted dairy product intake. The patients went out at least once every day, and had no family history of rickets. Physical examinations showed short stature (-1.8 to -2.8 SD) and relatively low body weight (-0.4 to -1.7 SD). Wrist swellings were found in two patients, and rachitic rosary in one. Radiographic surveys of the wrists and knees demonstrated evidence of rickets such as frayed and widened metaphyses. Laboratory findings showed decreased levels of serum inorganic phosphorus (2.5 to 3.4 mg/dl) and increased levels of ALP (1,113 to 2,027 U/l), iPTH (287 to 428 pg/ml), and $1,25(\text{OH})_2\text{D}$ (130 to 200 pg/ml). The serum levels of 25OHD were relatively low (13 to 15.2 ng/ml). The serum levels of calcium were not apparently reduced (8.6 to 9.2 mg/dl). The ratios of maximal renal tubular reabsorption to glomerular filtration rate (TmP/GFR) were not reduced (above 3.4 mg/dl). These patients began 1α -hydroxyvitamin D ($1\alpha\text{OHD}$) treatment (0.1–0.2 $\mu\text{g}/\text{kg}/\text{day}$). The dose was adjusted in accordance with serum and urine levels of calcium. It was tapered over several months, after laboratory findings, such

Table 1 Clinical features

Patient No.	1	2	3	4	5	6	7
Gender	female	female	male	male	male	female	male
Age (mo)	25	19	29	13	1	2	1
Complaint	leg bowing	leg bowing	leg bowing	seizure	seizure	seizure	irritability
Breastfeeding	+	+	+	+	+	+	+
Formula	-	-	-	-	+	+	+
Dietary restriction	-	-	dairy product	*	-	-	-
Going outside	daily	willingly	twice a day	sometimes	R	R	R
Height (SD)	-1.8	-2.8	-2.6	-0.5	-0.9	NA	-1.4
Weight (SD)	-1.2	-1.7	-0.4	-0.4	+ 0.6	NA	-0.9

*, Dietary change before administration; R, going outside restricted; NA, not available. Part of this table was reported in reference 5.

Table 2 Biochemical parameters

Patient No.	1	2	3	4	5	6	7
Ca (8.4–10.0 mg/dl)	8.6	9.2	8.6	4.2	6.4	5.3	5.2
IP (4.0–6.2 mg/dl)*	3.4	3.1	2.5	6.2	7.7	4.2	8.2
ALP (287–809 U/l)*	1,113	2,027	1,901	1,945	1,287	2,257	1,509
iPTH (10–60 pg/ml)	428	287	314	445	117	350	160
1,25(OH) ₂ D (20–60 pg/ml)	130	130	200	56	118	22.9	15
25OHD (9.0–33.9 ng/ml)	15.2	13	14.9	7.4	8	<4	3
Mother's 25OHD (9.0–33.9 ng/ml)	NA	NA	NA	NA	NA	6	10
TmP/GFR (2.3–4.3 mg/dl)	>5	4.5	3.4	>5	NA	NA	NA

The reference ranges in adults are shown in parentheses, except for IP and ALP. *The reference ranges of IP and ALP at the ages of 1 to 2 yr are described for IP and ALP. NA, not available. Part of this table was reported in reference 5.

as ALP, iPTH, and inorganic phosphorus, and radiographic alterations associated with rickets started to normalize. Upon improvement of the above parameters, we discontinued the medication. In addition, we followed up the patients for 4 to 10 mo and verified no deterioration in their condition after discontinuance in order to exclude inherited rickets.

Of the four patients with tetany, three, previously reported (5), were 1 to 2 mo old and the other was 13 mo old. Seizures occurred in three patients, and irritability in one. Three infants were both breast- and bottle-fed, and did

not often go outside due to their parents' concerns about the weather, hemangioma of the face, or for no particular reason, respectively. They showed no leg bowing, rachitic rosary, or wrist swelling. Radiographic surveys of their wrists demonstrated no evidence of rickets. The 13-mo-old toddler had only been breast-fed, but ate food without any restriction. However, he often ate out or ate retort-pouch foods for several days before his administration due to his mother being in poor health. He showed no leg bowing, but radiographic surveys demonstrated evidence of mild rickets. Laboratory findings of the four patients with tetany showed decreased levels of

serum calcium (4.2 to 6.4 mg/dl) and increased levels of ALP (1,287 to 2,257 U/l) and iPTH (117 to 445 pg/ml). The serum levels of 25OHD had clearly decreased (below 8 ng/ml). The serum level of 1,25(OH)₂D was elevated in one patient, but not in the others. The serum level of inorganic phosphorus decreased in only one patient. We treated these patients with calcium and/or 1 α OHD.

Discussion

The current report showed two major clinical presentations, rickets and tetany in vitamin D deficiency. Of note, rickets can be associated with even relatively low levels of 25OHD (13 to 15.2 ng/ml). These values are within the reference range in the laboratory where we requested the 25OHD measurement. However, the clinical and radiographic findings, increased levels of ALP and iPTH, and low levels of inorganic phosphorus, indicated rickets, although they had apparently no extreme restriction of diet and/or sunlight exposure. The high levels of 1,25(OH)₂D imply that even relatively low levels of 25OHD can synthesize 1,25(OH)₂D, although they are actually not able to maintain the phosphorus homeostasis. The serum levels of calcium were preserved by increased iPTH and 1,25(OH)₂D. Optimal vitamin D status has been suggested to suppress parathyroid hormone (PTH) concentrations. Many studies have reported an expected inverse association between serum 25OHD concentrations and serum PTH concentrations (8–11), therefore, elevated PTH concentrations are caused by the compensation mechanism of calcium homeostasis and can be a hallmark of vitamin D deficiency. These studies suggested that serum 25OHD should be more than 15 ng/ml, 20 ng/ml, or probably even higher to achieve the optimum PTH levels. Moreover, it is indicated that the variability in serum 25OHD measurements and the normal values between laboratories make it difficult for clinicians to

judge their patients vitamin D deficient (12). Diagnosis of vitamin D deficiency should be made comprehensively, from not only the value of 25OHD, but also the values of iPTH, ALP, calcium, and inorganic phosphate, as well as radiographic findings, since the appropriate normal range of 25OHD has not yet been agreed.

It has been recognized that the serum level of 25OHD exhibits an annual cyclic variation, with a peak in late summer and a nadir in late winter. This variation is mostly considered to be due to a seasonal variation in the amount of solar ultraviolet-B radiation, which is higher in summer than in winter. Seasonal variations in 25OHD concentrations have been found recently not only at higher latitudes but also even at lower ones, such as Florida at 25°N and Sao Paulo at 23°S latitude (13, 14). All three patients with rickets due to vitamin D deficiency resided in the Kansai region at a temperate latitude (35°N) in Japan. Therefore, 25OHD concentrations of the people in the Kansai region could be lower in winter than those in summer. However, It is very difficult to determine exactly when a person develops rickets because it takes a relatively long time. The depletion of vitamin D stores proceeds the following conditions step by step over a long period: decreasing calcium and phosphate availability, defects in bone mineralization, the typical appearance of rickets at the growth plate and the gradual softening of bone, and bone deformity in association with weight-bearing. Thus, we cannot specify a season during which rickets occurs. All the three patients with rickets due to vitamin D deficiency went out every day and did not avoid exposure to the sun. However, it is well known that an extremely imbalanced diet causes vitamin D deficiency. The rickets due to vitamin D deficiency in patient 3 might have been related to restriction of dairy products. No diet restrictions were noted in the patients 1 and 2 during this study. All the patients with rickets had no obvious restriction of sunlight exposure or extremely imbalanced diet,

suggesting that clinicians should pay attention to the possibility of vitamin D deficiency even if the history of present illness includes no high risk for it.

Studies from South Africa (15) and Nigeria (16) suggested that rickets was attributable to low dietary calcium intakes, estimated to be 200 mg/day, and not vitamin D deficiency. These diets were high in unrefined cereal, containing phytates which impairs calcium absorption. Calcium supplements alone or in combination with vitamin D were equally effective at treating rickets and were more effective than vitamin D alone. A study from the U. S. A. suggested that low calcium intakes might also be responsible for rickets among mainly African American toddlers (17). Eighty-three percent ate a diet low in dairy products, and serum levels of 25OHD were above 15 ng/dl in 78% patients. On the other hand, two patients with rickets in the current report did not restrict dairy products, and radiographic and laboratory findings improved after 1α OHD treatment. Thus, the clinical courses are not compatible with that of dietary calcium deficiency as described above.

In contrast, all four patients with tetany had profound hypocalcemia and their 25OHD status was undoubtedly low (< 4 to 8 ng/ml). The three young infants were not often taken out and the two of their mothers of them had hypovitaminosis D, probably leading to inadequate 25OHD synthesis in the skin and low transfer of 25OHD across the placenta. This resulted in the low values of 25OHD in their infants. Maternal vitamin D status during pregnancy has been investigated for its involvement in neonatal calcium homeostasis (6). Formula with a high phosphorus content presumably maintains the level of inorganic phosphorus and might accelerate hypocalcemia because of the high phosphate load. No evidence of rickets is probably due to the absence of apparently low levels of serum inorganic phosphorus. The cause of hypovitaminosis D in the 13-mo-old infant was

not clear, but could be partly due to the fact that he only sometimes went outside in winter. Hypocalcemia might have been due to vitamin D deficiency and high phosphate load. The serum levels of $1,25(\text{OH})_2\text{D}$ were not elevated in three of four patients with tetany, which was certainly due to an inadequate substrate of 25OHD available for its conversion to $1,25(\text{OH})_2\text{D}$.

The patients with rickets due to vitamin D deficiency began 1α OHD treatment. It took several months for laboratory findings and radiographic findings of metaphyses to improve. Moreover, we followed up the patients for 4 to 10 mo after we discontinued the medication. It is crucial to verify no deterioration in the above findings after tapering the dose and discontinuing the medication, because rickets due to vitamin D dependency, vitamin D resistance, and hypophosphatemia must be excluded.

In summary, we report seven Japanese clinical cases of vitamin D deficiency with tetany and rickets. These results indicate that vitamin D deficiency is not rare in Japan, and that relatively low levels of 25OHD (15.2 ng/ml or below) can cause rickets. Clinicians must therefore interpret the level of 25OHD cautiously.

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