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Case Report

A Case of Vitamin D Deficiency without Elevation of Serum Alkaline Phosphatase in a Carrier of Hypophosphatasia

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Abstract. Elevated serum alkaline phosphatase (ALP) is a screening marker for the diagnosis of vitamin D deficiency, which may fail to be diagnosed if serum ALP is not elevated. Here, we describe a case of vitamin D deficiency without elevation of serum ALP. A 1-year-old Japanese girl was referred to our hospital for the evaluation of genu varum. Her serum intact PTH level was elevated, while her serum ALP level was normal. Furthermore, her serum 25-hydroxyvitamin D level was reduced, and her urine phosphoethanolamine (PEA) level was mildly elevated. *ALPL* gene analysis revealed she was a heterozygous carrier of hypophosphatasia (c.1559delT). Serum intact PTH and urine PEA evaluations were helpful for diagnosing vitamin D deficiency and hypophosphatasia carrier status, respectively. Therefore, the possibility of vitamin D deficiency without elevation of serum ALP should be considered.

Key words: vitamin D deficiency, hypophosphatasia, ALPL, intact PTH, phosphoethanolamine

Introduction

Elevated serum alkaline phosphatase (ALP) level is an essential marker for the diagnosis of vitamin D deficiency (1). Some cases of vitamin D deficiency are diagnosed accidentally on the basis of elevated ALP levels. Therefore, cases without high ALP may be excluded from a diagnosis of vitamin D deficiency.

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Hypophosphatasia is a congenital skeletal disease caused by mutation of the *ALPL* gene, which encodes the ALP isozyme, tissue-nonspecific alkaline phosphatase (TNSALP) (2). Hypophosphatasia is characterized by severe reduction of ALP as well as various skeletal abnormalities such as rickets. Since most cases are transmitted as an autosomal recessive trait, those heterozygous for *ALPL* mutation are carriers who exhibit a low or normal ALP level (3).

Here, we describe a case of vitamin D deficiency without an elevated ALP level in a patient that proved to be a heterozygous carrier of hypophosphatasia.

Case Report

A 1-year-old Japanese girl was referred to our hospital for the evaluation of genu varum. She had no history of bone fractures. At her initial visit, her serum intact PTH level was elevated (273 pg/mL, normal range: 10–65 pg/mL) while her serum ALP, calcium, and inorganic phosphate levels were normal (527 U/L, normal range: 395–1289 U/L; 9.5 mg/dL, normal range: 8.8–10.6 mg/dL; 5.9 mg/dL, normal range: 3.8–6.2 mg/dL, respectively). Her percentage of tubular reabsorption of phosphate (%TRP) was elevated (96.9%, normal range: 80–95%). Her urine calcium/creatinine level was reduced (0.019, normal range: 0.035–0.80), and her urine cross-linked N-telopeptide of type I collagen (NTX) level was 1340 nmol BCE/mmol creatinine (normal range: 369–2385 nmol BCE/mmol creatinine). Additional measurement of serum 25-hydoxyvitamin D (25-OHD) was not performed, because of normal serum ALP levels. On limb radiography, calcification of epiphyses was detected, and both flaring and fraying of metaphyses were also detected slightly (Fig. 1). Therefore, the patient was initially diagnosed with spontaneously half-healed vitamin D deficiency rickets and was followed closely without treatment. However, 3 months later, her serum intact PTH level remained elevated and serum 25-OHD level was reduced (6 ng/mL, normal range: 20–100 ng/mL). The patient was subsequently diagnosed with vitamin D deficiency. The serum intact PTH level improved immediately after initiation of alfacalcidol administration and has not been elevated since the end of treatment. In addition, her serum ALP level decreased gradually (Table 1).

Although these courses of treatment support the diagnosis of vitamin D deficiency, the relatively low ALP level was atypical. Low serum zinc level, which is one of the causes of reduced ALP level, was not identified (71 μg/dL, normal range: 64–118 μg/dL). Mild elevation of the urine phosphoethanolamine (PEA) level

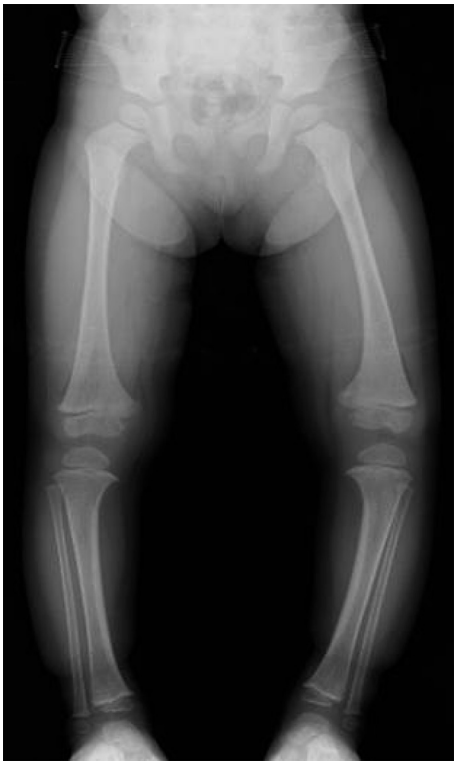

Fig. 1 Lower-limb radiograph. The epiphyses were calcified. The metaphyses were flared and frayed slightly.

(279.1 μmol/g creatinine, normal range: 83–222 μmol/g creatinine) suggested hypophosphatasia (4).

Therefore, we analyzed the *ALPL* gene for a diagnosis of hypophosphatasia. Genomic DNA was extracted from peripheral blood leukocytes of the patient and her parents after obtaining written informed consent. All coding exons and flanking introns of *ALPL* were analyzed using the PCR direct sequencing method. Primer sequences and PCR conditions are available on request.

An *ALPL* heterozygous mutation, c.1559delT, was detected in the patient and her father (Fig. 2), but no mutation was detected in her mother. The serum ALP level of her father was mildly reduced (84 U/L, normal range: 96–284 U/L) and that of her mother was normal (180 U/L). Therefore, the patient and her father were diagnosed as carriers

Table 1 Laboratory data

	At 1st visit	At diagnosis	1 year after stopping treatment	Reference range
Age (years)	1.8	2	3.3	
Serum				
Ca (mg/dl)	9.5	9.9	9.8	8.8–10.6
P (mg/dl)	5.9	6	5.9	3.8–6.2
ALP (U/l)	527	431	375	395–1289
Intact PTH (pg/ml)	273	192	54	10–65
25-OHD (ng/ml)	ND	6	ND	20–100
Urine				
PEA (μmol/gCr)	ND	279.1	308.6	83–222

PEA, phosphoethanolamine; ND, not done.

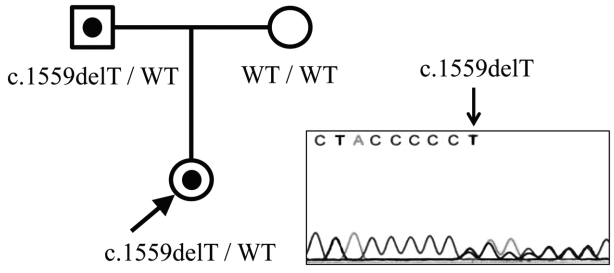

Fig. 2 *ALPL* analysis in the patient's family. Black dots indicate heterozygous *ALPL* carriers (c.1559delT).

of hypophosphatasia. Her father had no history of bone fracture or abnormal skeletal findings. It was unknown whether he had presented genu varum during childhood.

Discussion

This is the first report of vitamin D deficiency without an elevated serum ALP level in a carrier of hypophosphatasia.

Vitamin D deficiency is reemerging worldwide (5), and elevated serum ALP is a hallmark of this disease (1). Vitamin D deficiency may fail to be diagnosed if serum ALP is not elevated. However, simultaneous measurement of the serum intact PTH level is helpful for diagnosis.

Measurement of urine PEA was useful for the diagnosis of hypophosphatasia in the present case. While severe elevation of the urine PEA level (approximately >1000 μmol/g creatinine in childhood) is detected in patients with hypophosphatasia, mild elevation suggests carrier status of this disease (3).

The *ALPL* mutation c.1559delT is the most common mutation in Japanese patients with hypophosphatasia (6). A homozygous c.1559delT mutation is involved in the perinatal lethal form of hypophosphatasia with a severe reduction in serum ALP (6). The heterozygous mutation is found in carriers who present various levels (either low or normal) of serum ALP without skeletal abnormality (3). Furthermore, urine PEA levels also range from normal to high in such individuals (3).

The frequency of carriers is predicted to be high (1/480) (3). Since vitamin D deficiency is reemerging, the present case should be kept in mind, as the possibility of such conditions occurring more frequently is high.

Vitamin D deficiency rickets was reported to be associated with the infantile form of hypophosphatasia in a 9-month-old boy (7). In that report, although the serum ALP level increased from 66 U/L at baseline to 400 U/L at diagnosis, it decreased soon after treatment. On the other hand, the present case was considered to be mild vitamin D deficiency because of the

mild elevation of serum ALP level and lack of clinical findings of active rickets.

In conclusion, an *ALPL* heterozygous mutation was detected in a patient with vitamin D deficiency without an elevated serum ALP level. Measurement of serum intact PTH and urine PEA levels is helpful for diagnosing vitamin D deficiency and identifying carriers of hypophosphatasia, respectively. The possibility of vitamin D deficiency without elevated serum ALP should be considered.

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