A Case of Vitamin D Dependency Type I

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Abstract. Vitamin D dependency type I is a disease characterized by hypocalcemia and rickets in early infancy. We report the case of a female patient diagnosed as having vitamin D dependency type I by the clinical features and the PTH loading test after a low calcium diet. The patient was referred to Osaka University Hospital when she was 2 years 2 months old. She had slight bowing of the legs but no hypocalcemia. Her serum concentrations of 25-hydroxyvitamin D (25OHD) and 1,25(OH)₂D were 18.1 ng/ml and 14 pg/ml, respectively. After 3 days on a low calcium diet, the PTH loading test was performed. Neither the low calcium diet nor the injection of PTH increased serum 1,25(OH)₂D levels, while serum 1,25(OH)₂D levels were significantly increased in normal controls. When active vitamin D metabolites were not administered, serum alkaline phosphatase (ALP) and PTH increased gradually to 1090 U/l and 1120 pg/ml, respectively. After administration of a physiological dose (0.08 μg/kg/day) of 1α-hydroxyvitamin D₃ (1αOHD₃), the serum ALP and PTH levels returned to normal.

The blunted response of serum 1,25(OH)₂D concentration to the PTH loading test as well as to the low calcium diet, and the necessity for a physiological dose of 1αOHD₃, suggest that she had a partial defect in renal 25OHD₃-1α-hydroxylase activity.

Key words: vitamin D dependency type I, 1α-hydroxylase, 1αOHD₃, Ellsworth-Howard test

Introduction

1,25(OH)₂D₃ is a physiological vitamin D metabolite which has potent biological activity. 1,25(OH)₂D₃ is synthesized from 25-

hydroxyvitamin D₃ (25OHD₃) in the kidney by 25OHD₃-1α-hydroxylase (1α-hydroxylase). 1, 25(OH)₂D₃ binds its cognitive receptor in target cells and activates the receptor. Thereafter, the 1,25(OH)₂D₃-receptor complex binds specific DNA sequences, namely vitamin D responsive element [1,2] in 1,25(OH)₂D₃-responsive gene promoter, and displays its biological activities.

Vitamin D dependency type I, first re-

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ported by Prader et al. [3] in 1961, is a disease characterized by hypocalcemia and rickets in early infancy. In this disease, a pharmacological dose of vitamin D or a physiological dose of active vitamin D metabolites is required to cure the hypocalcemia and rickets. This condition is transmitted in autosomal recessive form. Fraser et al. [4] reported in 1973 that 1α -hydroxylase deficiency was associated with its pathogenesis. Subsequent studies indicated a new type of vitamin D resistant rickets where the disorder of $1,25(\text{OH})_2\text{D}_3$ receptor response in the target organ contributed to the pathogenesis [5,6]. This is called vitamin D dependency type II. Determination of serum $1,25(\text{OH})_2\text{D}$ levels appears to be the most reliable means for distinguishing the two disorders. The patient with vitamin D dependency type I shows a low serum $1,25(\text{OH})_2\text{D}$ level (2-12 pg/ml) [7]; in contrast, vitamin D dependency type II shows high serum $1,25(\text{OH})_2\text{D}$ (66-916 pg/ml) [8].

The complementary DNA for $1,25(\text{OH})_2\text{D}_3$ receptor was identified. This finding enables us to verify the diagnosis of vitamin D dependency type II, and several cases have been reported which were diagnosed by identification of point mutations [9,10]. There is no report at present in which the mutation of 1α -hydroxylase in a patient with vitamin D dependency type I is ascertained. In this paper, we have investigated the response of serum $1,25(\text{OH})_2\text{D}$ concentration after PTH loading and low calcium diet in a patient who was suspected to have vitamin D dependency type I, to confirm the pathogenesis of this type of vitamin D dependency.

Case Report

The high serum value of ALP was detected in a laboratory test before immunization, when the patient was 1 year 1 month old. 1α -hydroxyvitamin D_3 ($1\alpha\text{OHD}_3$) ($0.06 \mu\text{g/kg/day}$) was administered for a month, but did not normalize the serum ALP levels. She was then admitted to the Chiba University Hospital. On admission, she had slight bowing deformity of the legs, and rachitic change was evident in roentgenograms (Fig. 1. A). In laboratory data, hypocalcemia, hypophosphatemia, high levels of ALP and PTH, and generalized aminoaciduria were observed. She was tentatively diagnosed as vitamin D dependency type I, and treated with $1\alpha\text{OHD}_3$ ($0.1 \mu\text{g/kg/day}$), after which these

Fig 1. (A) Roentgenogram on admission at Chiba University Hospital. Rachitic changes including framing, widening, and cupping are seen in metaphyses of distal femur and proximal tibia. (B) Roentgenogram on admission at Osaka University Hospital. The rachitic changes are improved.

Table 1. Laboratory data on admission

TP	7.2 g/dl	WBC	11700/mm ³	m-PTH	426.6 pg/ml
Alb	2.6 g/dl	RBC	$577 \times 10^4/\text{mm}^3$	intact-PTH	67 pg/ml
BUN	16 mg/dl	Hb	11.3 g/dl	Serum cAMP	42.7 pmol/ml
Cr	0.4 mg/dl	Serum β_2 -MG	1.4 $\mu\text{g/ml}$	Urinary cAMP	66.5 nmol/mgCr
Ca	9.6 mg/dl	Urinary β_2 -MG	134 $\mu\text{g/l}$	25OHD	12.3 ng/ml
Ca ²⁺	1.22 mmol/l	Ccr	79.7 ml/min/1.73m ²	$1,25(\text{OH})_2\text{D}$	51 pg/ml
P	5.4 mg/dl	Blood gas		$24,25(\text{OH})_2\text{D}$	0.45 ng/ml
Mg	2.0 mEq/l	PH	7.46	%TRP	81.6 %
ALP	534 U/l	HCO ₃	17.0 mEq/l		
GOT	32 U/l	B.E.	-5.4		
GPT	4 U/l				

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abnormalities disappeared. She was then referred to Osaka University Hospital at 2 years 2 months of age. Her father's parents were first cousins. Her parents were healthy, and blood and urine tests did not indicate any abnormalities. Her height was 85 cm (-1SD) and her weight was 11.4 kg (-1SD). A slight bowing deformity was recognized in her lower extremities (Fig. 1. B), but no rachitic change was observed on radiographic examination. Table 1 shows the laboratory data on admission when $1\alpha\text{OHD}_3$ treatment had been stopped for 2 weeks. Serum ALP level was slightly elevated (534 U/l), but serum calcium and phosphorus and renal function were within the normal ranges. Although the serum PTH was normal, plasma cAMP was increased and the value of %TRP was decreased. Judging from the clinical course at Chiba University Hospital (Fig. 2), it appeared that the elevated serum ALP level and hyperparathyroid-function on admission to Osaka University Hospital might have been derived

from subclinical hypocalcemia after the cessation of $1\alpha\text{OHD}_3$ treatment. Although the serum 25OHD and $1,25(\text{OH})_2\text{D}$ concentrations, which were measured using chick embryonal receptor as previously reported [11], were normal at that time, serum $1,25(\text{OH})_2\text{D}$ was decreased to 14 pg/ml after 3 weeks cessation of $1\alpha\text{OHD}_3$. These observations suggested that she had a disorder in 1α -hydroxylase activity. To confirm this, we studied the serum $1,25(\text{OH})_2\text{D}$ concentration after the Ellsworth-Howard test (EH test) and a calcium restricted diet, because PTH and hypocalcemia are known to stimulate 1α -hydroxylase activity [12].

The Ellsworth-Howard test

Before the EH test, a low calcium diet containing 200 mg of calcium and 400 mg of phosphorus was given for 3 days. Then 100 U/m² of 1-34 human PTH (Toyo Jozo) was infused intravenously, according to the guide-

lines of this provocation test [13]. There was a significant change in urinary cAMP excretion (15.3 times elevation at one hour after loading), although no significant changes were observed in the amount of renal phosphorus excretion (Fig. 3). Plasma cAMP levels also increased in response to the injection of PTH. Ishida et al. [14] pointed out that the change of plasma cAMP is a useful indicator for children in the EH test. They considered that more than 100 pmol/ml in the highest plasma cAMP value or an increment of more than 50 pmol/ml after PTH injection in the plasma cAMP was a positive reaction. The highest plasma cAMP of our patient was 376 pmol/ml and it increased by 357.6 pmol/ml after PTH injection. From these results, we concluded that her response to exogenous PTH was normal. There were no significant changes in the serum 1,25(OH)₂D concentration after 1-34 human PTH loading in the patient, while a 46% rise was observed in adult controls (Fig. 4).

Change of serum 1,25(OH)₂D levels after low calcium diet

Figure 5 shows the change of serum 1,25(OH)₂D levels after 3 days on a low calcium diet containing 200 mg of calcium and 400 mg of phosphorus. Two patients diagnosed as idiopathic hypercalciuria were studied as controls. One was 4 years and the other 9 years old. In the patient with vitamin D dependency type I, there was no significant change in serum 1,25(OH)₂D levels, while significant increases in serum 1,25(OH)₂D concentration were observed in the controls.

Fig 4. Time course of serum 1,25(OH)₂D concentration after PTH injection. The values in ten adult volunteers are shown as the mean $\pm$ SD.

Fig 3. Result of Ellsworth-Howard test.

One hundred U/m² of 1-34 human PTH was infused intravenously. Changes of urinary phosphorus, urinary cAMP and plasma cAMP are shown. Open bars indicate values before PTH injection, and closed bars indicate those of urinary phosphorus and urinary cAMP after PTH injection. Shadow area represents the range of response of plasma cAMP in the control.

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Fig 5. Serum 1,25(OH)₂D concentration after 3 days on a low calcium diet containing 200 mg of calcium and 400 mg of phosphorus. Two patients with idiopathic hypercalciuria were studied as controls.

Clinical course after discharge

For the next 6 months, the patient was followed-up in our outpatient clinic without any medication to rule out transient vitamin D deficiency. Although the serum calcium level did not change, serum ALP and PTH increased and serum phosphorus decreased. After administration of 1 α OHD₃ (0.08 μ g/kg/day), the serum ALP, PTH, and phosphorus levels returned to normal (Fig. 2).

Criteria of vitamin D dependency type I

Table 2 shows the revised criteria of vitamin D dependency type I [15]. Our patient satisfied all the criteria in paragraphs A and C.

Discussion

Vitamin D dependency type I is a rare inborn error of metabolism transmitted in autosomal recessive form. A deficiency of 1 α -hydroxylase, which involves the conversion of 25OHD₃ to 1,25(OH)₂D₃, has been reported to explain the pathogenesis of this disease. The clinical and radiological features and biochemical data are similar to those of vitamin D-deficient rickets except for serum 25OHD concentration. In our case,

evidence of normal serum 25OHD concentration before medication and deterioration of serum ALP and PTH concentrations after cessation of a physiological dose of 1 α OHD₃ exclude the diagnosis of vitamin D-deficient rickets.

Despite the consensus that the defect of 1 α -hydroxylase activity is the main abnormality in vitamin D dependency type I and the fact that it has been proved in pigs [16], there have been no reports which investigated it directly in humans. In this study, we tried to assess the 1 α -hydroxylase activity through the EH test and a low calcium diet, because PTH and a low calcium diet are known to stimulate this activity [17]. In the EH test and on a low calcium diet, there was no increase of serum 1,25(OH)₂D level in our patient, while a significant increase was observed in controls. Although there was a good response of cAMP to PTH, no phosphaturic effect was observed such as is seen in pseudohypoparathyroidism type II. This phenomenon, which was reported earlier in patients with vitamin D dependency type I [7], and in vitamin D deficient rats [18], is probably caused by secondary hyperparathyroidism.

In patients with vitamin D dependency type II, the clinical manifestations are similar to those of vitamin D dependency type I. However, a high level of serum 1,25(OH)₂D and the requirement of pharmacological doses of active vitamin D metabolites are thought to

Table 2. Vitamin D Dependency type I

Criteria for diagnosis	
(A) Clinical characteristics	
i)	Early onset
ii)	Rachitic change on roentgenogram
iii)	Hypocalcemia
iv)	Hyperalkalinephosphatasemia
v)	Normal renal function
(B) Unsuccessful therapy	
i)	3000-4000 U of vitamin D p.o. every day for 4 weeks
(C) Successful therapy	
i)	Physiological dose of active vitamin D metabolites every day
(D) Others	
i)	Low serum concentration of 1,25(OH) ₂ D
ii)	Function of renal tubules restored by administration of active vitamin D

be useful to distinguish the two diseases. The serum 1,25(OH)₂D concentration in our patient was in the low normal range through the follow-up period, and a physiological dose of 1 α OHD₃ was sufficient to cure her rickets. Therefore we diagnosed her as vitamin D dependency type I.

Recently, linkage analysis using a large family of vitamin D dependency type I patients has demonstrated that the gene responsible for the disease is located on chromosome 12 at q14 [19]. Thus it may be possible in the future to detect carriers and to make an early diagnosis of vitamin D dependency type I before the onset of serious hypocalcemia.

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