

A CASE OF RICKETS WITH NORMAL SERUM LEVEL OF 1, 25-(OH)₂D AND LOW 25-OHD^{*}

By

Hiroshi KASHIWA¹⁾, Yoshikazu NISHI¹⁾, Tomofusa USUI¹⁾
and Yoshiki SEINO²⁾

1) *Department of Pediatrics, Hiroshima University School of Medicine, Hiroshima 734, Japan*

2) *Department of Pediatrics, Osaka University Hospital, Osaka 553, Japan*

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Correspondence to Dr. Y. Nishi, Department of Pediatrics, Hiroshima University
School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734, Japan

ABSTRACT

In a patient with rickets developed after bowel surgery, we found a low serum concentration of 25-OHD and normal serum concentration of 1, 25-(OH)₂D. Oral administration of 1 α -OHD₃ resulted in dramatic improvement of rickets and normalization of serum 25-OHD and calcium. These findings suggest that 25-OHD deficiency may play an important part in the pathogenesis of osteomalacia.

INTRODUCTION

It is generally believed that the biological actions of vitamin D depend on the presence of 1, 25-(OH)₂D and the manifestations of vitamin D deficiency, including rickets, are due to a quantitative deficiency of this metabolite¹⁾. However, this concept appears not necessarily to be true since normal or high plasma concentrations of 1, 25-(OH)₂D and low plasma concentrations of other metabolites of vitamin D such as 25-OHD and 24, 25-(OH)₂D have been documented in patients treated with anticonvulsants who develop osteomalacia²⁾, as well as in patients with untreated nutritional osteomalacia³⁾.

We report a patient who had a jejunioileostomy for congenital jejunal atresia, then developed osteomalacia after bowel surgery and was found to have a low serum concentration of 25-OHD and a normal serum concentration of 1, 25-(OH)₂D.

CASE REPORT

This female infant was born to a healthy mother after an uncomplicated pregnancy of 33 weeks and a normal delivery. Birth weight was 1,770 grams and length was 38.0 cm. She vomited frequently when she took milk on the first day. Radiological examination of the abdomen revealed localized gas in the epigastrium, the so called "triple bubble sign". On the second day, a laparotomy was performed under the diagnosis of congenital jejunal atresia (apple peel atresia type), about sixty centimeters of necrotic jejunum near Treitz's ligament was removed, and a jejunioileostomy (end-to-end) was performed. After bowel surgery, she did not gain well.

At three months of age, her parents noticed softness of the skull. She was transferred to us for evaluation of the softness of the skull and failure to thrive. As far as could be determined, no relatives were similarly affected.

^{*}) 柏 弘, 西 美和, 白井朋包, 清野佳紀: 血清中 1, 25-(OH)₂D 正常, 25-DHD 低値を示したくる病の一症例

On physical examination, her weight was 3,820 grams and height 51.5 cm. She had extensive craniomalacia and a rachitic rosary. There was no steatorrhea. Radiological findings of bones were typical of rickets: (1) generalized osteoporosis, (2) spread, frayed, and cupped distal ends of long bones, (3) rachitic changes of costochondral junctions and (4) absence of proximal tibia centers and of tarsal bones in spite of the presence of distal femoral centers. Laboratory data showed a serum calcium concentration of 7.0 mg/dl, serum phosphorus of 4.6 mg/dl and serum alkaline phosphatase of 3,327 IU/l. Plasma parathyroid hormone was 3.2 ng/ml (normal 0.5 to 1.0 ng/ml). The renal tubular reabsorption of phosphorus was 47.0%. Blood pH ranged from 7.25 to 7.35 and the concentration of bicarbonate from 15.8 mmol/l to 18.2 mmol/l, urinary pH was 5.5 to 6.0. It appeared that this metabolic acidosis was due to a bicarbonate wasting form of renal tubular acidosis. In addition, there was partial aminoaciduria, but no glycosuria or proteinuria.

The serum 25-OHD level was 4.0 ng/ml (normal 10 to 30 ng/ml), and the 1,25-(OH)₂D level was 54.0 pg/ml (normal 44.7 to 99.3 pg/ml), which were measured by the competitive protein binding assay^{4,5}. The plasma copper level was 105 μg/dl (normal 53 to 108 μg/dl) and zinc 80 μg/dl (normal 66 to 94 μg/dl). The other laboratory data, including liver and renal function tests and serum total protein, were all within the normal range.

The patient was started on 0.5 μg of 1α-OHD₃ (Chugai Pharmaceutical Co. Ltd, Tokyo, Japan) per day, which was the only change in the diet. Two months of therapy resulted in dramatic improvement with disappearance of craniomalacia and rachitic rosary and all radiographic evidence of rickets, the bone age was normal. The serum calcium concentration increased to 8.2 mg/dl and serum phosphorus to 6.1 mg/dl. The serum alkaline phosphatase decreased to 570 IU/l. The serum 25-OHD level was increased to 10.4 ng/ml, the 1,25-(OH)₂D was 81.4 pg/ml, and the 24,25-(OH)₂D was 3.1 ng/ml (normal 1.3 to 2.9 ng/ml). In addition, %TRP rose to 70.0%, metabolic acidosis subsided and the plasma PTH level decreased to 1.3 ng/ml. The growth rate became normal.

DISCUSSION

The various forms of rickets can be divided into two main groups: (1) those due to deficiency of active vitamin D metabolites, (2) those due to target cell abnormality. The former includes vitamin D deficiency (absence of sunshine or dietary lack), vitamin D malabsorption, liver disease, anticonvulsant drugs, renal disease and vitamin D dependency (1-OHase abnormality)⁶.

In this case, the factors contributing to rickets were prematurity, vitamin D deficiency (inadequate sunshine exposure and dietary lack), and vitamin D malabsorption due to bowel surgery. Some patients with rickets were reported to have normal or high plasma concentrations of 1,25-(OH)₂D and low plasma concentration of 25-OHD and 24,25-(OH)₂D^{2,9}. It is of interest that the manifestations of vitamin D deficiency are likely to be the result of low serum concentration of 25-OHD or 24,25-(OH)₂D, which was not measured in this patient before therapy, but not 1,25-(OH)₂D.

The normal concentration of 1,25-(OH)₂D may represent an appropriate 1α-hydroxylation to hypocalcemia and secondary hyperparathyroidism. The serum 25-OHD is decreased since its supply may not be sufficient and it is used to biosynthesize adequate quantities of 1,25-(OH)₂D.

The small for gestational age infants can develop rickets and osteoporosis while receiving weight-related doses of vitamin D recommended for term infants, as well as adequate calcium supplements⁷. The premature infants are known to have an increased susceptibility to the development of rickets due, in part, to in-utero calcium deprivation and the increased requirement of vitamin D for rapid growth^{8,9}.

Endogenous vitamin D synthesis is normally the major source of circulating serum 25-OHD¹⁰. However, she had been hospitalized after birth without adequate exposure to sunlight, which stimulates endogenous vitamin D synthesis. This abnormal circumstance also played a role in the low level of 25-OHD concentration.

Moreover, after operation our patient received inadequate vitamin D because of the combination of parenteral nutrition without vitamin D supplements and only small amounts of milk.

However, since about 40 days after operation she was fed an adequate amount of milk formula containing approximately 440 IU vitamin D, 0.45 grams of calcium, and 0.30 grams of phosphorus per day, which are sufficient for the recommended dietary allowance¹¹⁾. Vitamin D, calcium, and fat in the diet are absorbed from the upper portion of the gastrointestinal tract. Bile acids are essential for the absorption of vitamin D in man and interruption of their enterohepatic circulation by resection of the small intestine may reduce the absorption of dietary vitamin D and 25-OHD undergoing enterohepatic circulation¹²⁾, even when the recommended dose of vitamin D is given orally. Thus, in our patient impaired absorption of vitamin D and calcium was also one of the important contributing factors to rickets.

After 1 α -OHD₃ therapy, 1, 25-(OH)₂D is increased by 25-hydroxylation of 1 α -OHD₃ in liver. The increase of serum level of 25-OHD after therapy suggests that the conversion of 25-OHD to 1, 25-(OH)₂D is decreased since 1, 25-(OH)₂D is sufficient from the 25-hydroxylation of exogenous 1 α -OHD₃. In addition, 24, 25-(OH)₂D may be increased since the activity of 24, 25-hydroxylase increases during treatment with 1 α -OHD₃¹³⁾. These findings are responsible for the dramatic improvement of rickets in this patient.

It seems that 1, 25-(OH)₂D is not the sole biologically active metabolite of vitamin D in man. Our case supports this hypothesis. Finally, we suggest, again, that the rickets in this case was due not only to calcium deprivation, but also the low concentration of 25-OHD or possibly, of some other metabolites of vitamin D such as 24, 25-(OH)₂D.

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