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Original Article

Vitamin D-Dependent Rickets: Eight Cases

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ABSTRACT

Objective: *Vitamin D is essential for bone development and health, and deficiency resulting in rickets and skeletal deformities is seen mainly during rapid growth. Hereditary vitamin D dependent rickets type I and type II rickets is a very rare form of rickets, characterized by 1-alpha-hydroxylase deficiency or end-organ resistance to vitamin D. We aimed to investigate, clinical and laboratory characteristics of eight cases with Vitamin D-dependent rickets (VDRR).* ***Method:*** *The mean age of patients during diagnosis was 2.6 years. Excluding one patient, others were males (87.5%).* ***Results:*** *Mean laboratory values during referral was calcium 7.5±1,5 mg/dl, phosphorus 4±1.2 mg/dl, alkaline phosphatase (ALP) 1679±641 U/L and parathyroid hormone (PTH) 524±498 pg/ml. Patients received 1.2 µg/kg/day calcitriol. During follow-ups serum ALP and PTH values of patients turned to normal levels.* ***Conclusion:*** *In rickets, cases with persistent increased serum ALP and PTH levels it will be appropriate to investigate serum 25 (OH) D levels in cases diagnosed with vitamin D-dependent rickets even though hypocalcaemia is absent. Administration of adequate doses of calcitriol in some cases is able to clinical and laboratory values return to normal.*

Key words: Rickets, vitamin D, child

Vitamin D Bağımlı Raşitizm: 8 olgu

ÖZET

Amaç: *Vitamin D kemik gelişimi ve sağlığı için gereklidir. D vitamini eksikliği raşitizmle sonuçlanır ve genel olarak hızlı büyüme döneminde kemik deformiteleri görülür. Ailesel Tip1 ve tip2 vitamin D bağımlı raşitizm oldukça nadir bir raşitizm formudur, 1-alfa-hidroksilaz enzim eksikliği veya son organ direnci ile karekterizedir. D bağımlı raşitizmi (VDBR) olan sekiz vakanın klinik ve laboratuar özellikleri geri dönük olarak incelendi.* ***Yöntem:*** *Tanı anında hastaların yaş ortalaması 2.6 yaşında bulundu. Biri hariç diğerleri erkekti (% 87.5).* ***Bulgular:*** *Kabul sırasında laboratuar değerleri; kalsiyum 7.5±1,5 mg/dl, fosfor 4±1.2 mg/dl, alkalen fosfataz (ALP) 1679±641 U/L ve paratiroid hormon (PTH) 524±498 pg/ml. Hastalar ortalama 1.2 µg/kg/day kalcitriol almış, takiplerde serum ALP and PTH değerleri normal seviyelere dönmüştü.* ***Sonuç:*** *Raşitizmli hastalarda, serum ALP and PTH seviyeleri yüksek seyrediyorsa hipokalsemi olmasa bile vitamin VDBR araştırmak uygun olacaktır. Yeterli doz D vitamini uygulandığında klinik ve laboratuar düzelme sağlanabilir.*

Anahtar kelimeler: *Raşitizm, vitamin D, çocuk*

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INTRODUCTION

Vitamin D also is formed in the skin as a result of direct exposure to sunlight. The liver and kidneys convert vitamin D from food sources or sunlight to an active form called calcitriol. This vitamin has an important role in bone mineral homeostasis by promoting the transport of calcium and phosphate to ensure that the blood levels of these ions are sufficient for the normal mineralization of type I collagen matrix in the skeleton (1). Vitamin D deficiency results in rickets this situation is common in areas where reception is inadequate (2,3).

Vitamin D was discovered during the 20th century and since vitamin D3 was found to be endogenously produced by the body or that it could be obtained from nutrients, it was immediately used in the treatment of nutritional rickets. However in some cases a resistance was observed against pharmacological doses of Vitamin D and these cases were then classified as vitamin D resistant rickets (VDRR). In further studies, it was stated that rickets resistive against Vitamin D would source from hypophosphatemic rickets, calcium (Ca) intake deficiency or congenital Vitamin D metabolism disorders whereas a resistance against Vitamin D receptor is likely to exist (4,5). In contrast to classic vitamin D-deficiency rickets, a number of vitamin D-resistant rachitic syndromes are caused by acquired and hereditary defects in the metabolic activation of the vitamin to its hormonal form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), or in the subsequent functions of the hormone in target cells (1).

Clinical and laboratory characteristics of VDRR cases encountered a period of three years are represented here.

MATERIAL AND METHODS

Eight patients who were diagnosed with VDRR during their referral to our pediatric endocrinology outpatient clinic between September 2003 and November 2006 were studied as retrospective. Data related with age, gender and biochemical values of patients were obtained from their files. Therapies which were provided during referrals and clinical follow-ups were carefully scrutinized. Absolute clinical and biochemical improvement periods and the therapeutically dosage during the mentioned periods were recorded. The patients with nutritional rickets due to insufficient nutrition and secondary rickets emerging chronic disease or long-term intake of medication interfering with bone metabolism were excluded from this study. Serum 25 (OH) D concentration was measured by licit chromatographic HPLC method (HP Agilent 1200 series, chrom systems kit, Germany), HP A silent technologies 1200 series. Plasma PTH was measured by a chemiluminescent immunoassay (Immulite 2000, Siemens USA). Ca, P, ALP were measured end point read system with colorimetric spectrofotometric method (Roche Hitachi modular Analytics system, Germany)

RESULTS

The mean age of patients during diagnosis was 2.6 years (the smallest child was 6 months and the oldest child was 5 years old). Excluding one child (87.5%) all patients were male. Two of the cases were siblings. They referred to our clinic at autumn and winter seasons. Mean laboratory values during application were as the following: Ca 7.5±1.5 mg/dl, phosphor 4±1.2 mg/dl, ALP 1679±641 U/L and PTH 524±498 pg/ml, excluding two patient whom were within the normal limits, calcium levels were low. Serum P was found low in another three patients and a regular phosphor replacement was needed in one of the cases. Serum 25-OH vitamin D [25(OH) D] levels were within the normal limits. 1.25 dihydroxy vitamin D [1. 25 (OH) 2D] level was found above the normal values in 2 patients and low in 2 patients out of 5 (Table 1). There was widening at the wrists of all of patients, and rachitic rosary, bell-shaped chest, muscle weakness, hypotonia in 5 cases (Figure 1). Expansion of the metaphysis, irregularity of the metaphyseal margin, a brush–like appearance, cupping and general osteopenia which typical radiological findings were

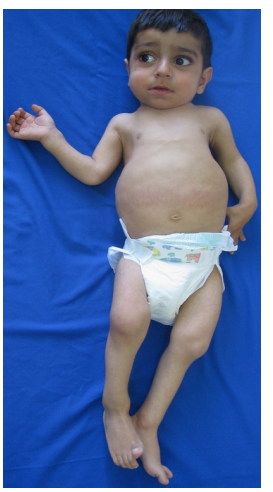

Figure 1*. The classic finding of rickets; widening at the wrists, rachitic rosary, bell-shaped chest, bone deformities of extremities and hypotonia.*

Table 1. *Mean laboratory values during diagnose and following of patients with VDDR.*

Case No	Diagnosed age(year)	Gender	Calcium (mg/dl)	Phosphor (mg/dl)	ALP (U/L)	PTH (U/L)	25(OH)D (µg/L)	1.25$(OH)_2$D (pg/ml) (30-65)	Radiological finding	Follow up (month)
1	0.5	male	8.1	3.4	2027	1347	30	_	yes	36
2	0.5	male	7.4	4.2	1374	346	42,5	_	yes	12
3	4.5	male	9	5.6	1410	84	43	150	no	24
4	3	male	8,9	5.5	941	102	22	120	no	24
5	0.9	female	6.7	2	3090	592	80	20	yes	29
6	4	male	7.8	4.2	2027	1347	34	_	yes	12
7	2	male	4	2.7	1152	187	33	15	yes	24
8	5	male	8.1	4.1	1414	189	22,9	66	no	12

detected in all cases below two years-old (Figure 2), and rachitic pneumopathic findings were present such as expansions in the costochondral junctions (rachitic rosaries) rachitic on the chest radiograph and fractures of the long bones resulting from thinning of the cortex due to general osteopenia in one case with severe rickets (Figure 3). There was no celiac disease, cystic fibrosis and other chronic disease that effected bone structure in any of our patients. A mean dose of 1.2 µg/kg/day (min.0.5 µg/day, max.2 µg/day) calcitriol was administered to patients. Cases were followed for a mean period of 18 months (average 12-36 months). Serum ALP and PTH values of patients during the follow-up term achieved normal values within a mean period equal to 13.5 months.

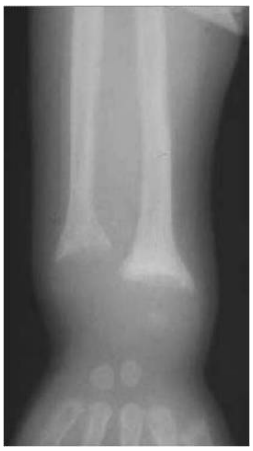

Figure 2. *Radiological appearance of cupping and irregularity of the metaphyseal margin in hand wrist.*

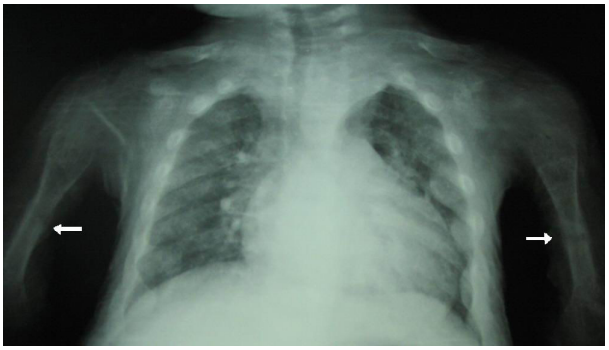

Figure 3. *Radiological appearance of rachitic pneumopathic findings and fractures of the upper extremities.*

DISCUSSION

If no improvement is observed in patients presenting with signs of rickets in spite of appropriate treatment, the metabolism disorders of Vitamin D should be kept in mind. Thus necessary tests should be planned for the etiologic differential diagnosis.

Vitamin D_3 (cholecalciferol), synthesized in the epidermis in response to UV radiation, and dietary vitamin D_2 (ergocalciferol, synthesized in plants) are devoid of any biologic activity. Vitamin D hormonal activity is due primarily to the hydroxylated metabolite of vitamin D_3, 1-alpha,25-dihydroxyvitamin D_3 (calcitriol), the actions of which are mediated by the vitamin D receptor (6-9). In the liver, vitamin D 25-hydroxylase catalyzes the initial hydroxylation of vitamin D at carbon 25; in the kidney, 1-alpha-hydroxylase catalyzes the hydroxylation and metabolic activation of 25-hydroxyvitamin D_3 into 1,25-dihydroxyvitamin D_3. The active metabolite 1.25 (OH) 2 D binds and activates the nuclear vitamin D receptor, with subsequent

regulation of physiologic events such as calcium homeostasis and cellular differentiation and proliferation (10).

Thanks to the effect of ultraviolet rays vitamin D_3 is synthesized in the skin or it can be easily obtained from especially fatty fishes. Risk factors related with Vitamin D deficiency are lack of Vitamin D replacement, premature state, low sunshine exposure, dermal pigmentation and malabsorption (4,5). The medical history of our nursing infants demonstrated restricted exposure to sun rays. These patients referred to our clinic during the autumn and winter seasons. None of the patients showed a history of Vitamin D supplementation. Although cholecalciferol given in adequate doses and duration for active rickets, it was not seen the clinical and biochemical improvement in patient presented here. So we thought might vitamin D dependent rickets, and we examined for differential diagnose. Some of our patients (5 cases) who at their suckling period displayed widening at their hand and foot wrists and rachitic rosary were also present. Radiological studies revealed irregularity on metaphies of long bones compatible to active rickets in hand wrist graphs of patients and calyx formation in various levels. There were multiple old fractions on his upper and lower limbs in two patients and there is uncleavaged fracture at her left wrist in ten month years-old girl. Older patients had complaints related with subjective joint and bone pain and were suffering from fatigue.

Vitamin D-dependent rickets type 1A is due to an enzymatic defect in synthesis of the active form of vitamin D caused by mutation in the CYP27B1 gene. VDDR1B is a form of rickets due to mutation in the gene encoding a vitamin D 25-hydroxylase; another enzyme necessary for the synthesis of active vitamin D. VDRR type 2A is caused by end-organ unresponsiveness of active vitamin D due to mutation in the gene encoding the vitamin D receptor. VDDR2B is an unusual form of end-organ unresponsiveness to active vitamin D due to an abnormal protein that interferes with the function of the VDR. In patients with Type I vitamin D dependent rickets, hypocalcaemia, hypophosphatemia, secondary hyperparathyroidism are present and ALP level is high while serum 25(OH) D level is normal and 1.25(OH) 2 D level is low (6-8). A resistance state at the receptor level can be pronounced for type II Vitamin D-dependent rickets (VDRR). During the first months patients may display classical rickets symptoms and have high 1.25(OH) 2 D level, as well 1.25(OH) 2 D level may be found normal (10-11).

In our patients, serum ALP and PTH levels were found high during referral. Serum calcium values were low and 25(OH) D levels were within normal limits in all patients. 1.25(OH) 2 D levels in patients who we were able to monitor were low in two patients out of five and above normal limits in three.

A mean dose of 1.2 µg/kg/day calcitriol was administered to patients (lowest dose 0.5 µg/ day, highest dose 2 µg/ day). Patients were followed up for an average of 18 months (minimum 12 months and maximum 48 months) and serum ALP and PTH levels returned to normal.

The patients with type II VDRR during the first months may display classical rickets symptoms and have high 1.25 (OH) 2 D levels. Poor responses to high dose calcitriol or inactivity can be present. Occasionally, rickets can be cured by pharmacologic dosages such as 15-30 µg/day or 1-6 µg/kg/day calcitriol. Calcium and phosphor levels are low, and 25 (OH) D is normal (8-10).

The earliest symptom among our patients was seen when the patients were 6 months old. One of our patients responded well after the dosage of calcitriol was increased to 2 µg /day while all of our patients succeed to respond to calcitriol therapy. Serum P was found low in another two patients and a regular phosphor replacement was needed later three months of initial calcitriol therapy in one of the cases whose respond of therapy was late for a year. However, we were not able to study 1.25(OH) 2 D levels in three patients, and therefore we failed to determine a definite type of rickets for them. Nevertheless, cases can be accepted as non-nutritional rickets patients because their values of 25 (OH) D are normal, and possibly not as type II VDRR; therefore patients can be considered as type I cases as they responded to therapy well in therapeutic doses, perhaps the degree of resistance was fairly low.

Consequently, in rickets cases with persistent increased serum ALP and PTH levels it will be appropriate to investigate serum 25 (OH) D levels in cases diagnosed with VDRR even though hypocalcaemia is absent. Administration of adequate doses of calcitriol in such cases shall allow clinical and laboratory values return to normal.

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