CASE SERIES

# Delayed diagnosis in Vitamin D-dependent rickets type II results in severe skeletal deformities

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## Abstract

Vitamin D-dependent Rickets Type II (VDDR-II) is a rare autosomal recessive disorder caused by a vitamin D receptor gene mutation, leading to end-organ resistance to 1,25-dihydroxyvitamin D 1,25(OH)2D. We aimed to investigate two cases of VDDR-II. Case 1 was of a 14-year old male, presenting with bone pains, bowing of legs, multiple bone deformities, and fractures since childhood. On examination, Chvostek's and Trousseau's signs were positive, and there was no alopecia. Case 2 was a 15-year old male who presented with pain in both legs since childhood and difficulty in walking lately. Upon investigation, it was found that bowing of legs, and Chvostek's and Trousseau's signs were positive. Both cases had severe hypocalcaemia, normal/low phosphate levels, and high alkaline phosphatase (ALP). Vitamin D levels were normal, and 1,25(OH) Vitamin D was very high, thus confirming the diagnosis of VDDR II. Both of the cases highlight a tremendous delay in diagnosis, resulting in severe adverse skeletal outcomes.

**Keywords:** Vitamin D, Delayed Diagnosis, Vitamin D - Dependent Rickets Type II (VDDR-II).

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## Introduction

Rickets, a metabolic bone disorder, could be either calciopenic resulting from calcium deficiency or decreased activity of vitamin D, or phosphopenic, which is mainly caused by renal phosphate wasting and is usually hereditary.[1] The decreased activity of vitamin D among patients with Calciopenic rickets might be due to lack of 25(OH)D conversion to the active metabolite 1,25(OH)2D, i.e., vitamin D-dependent rickets type 1 (VDDR-I), and type II (VDDR-II) in case of resistance to active vitamin D.

VDDR-II is a rare autosomal recessive disorder associated with Vitamin D receptor dysfunction due to gene mutations, leading to end-organ resistance to active metabolites. At birth, the affected children usually appear normal. It advances and becomes apparent within the first two years of life. A unique feature of the syndrome is alopecia, a marker of the disease's severity that is observed in approximately two-thirds of the cases.[2]

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## Case Report

Two cases of VDDR type II are described here.

### Case 1

A 14-year old male was presented in July 2019 with bone pain, multiple bone deformities (Figure-1A-C), and fractures since childhood. He also complained of intermittent diarrhoea. The patient underwent osteotomy thrice for correction of bone deformities. On examination, it was found that he had bowing of legs; Chvostek's and Trousseau's signs were positive, and there was no alopecia. There was a fracture of the right femoral shaft. Laboratory investigations showed severe hypocalcaemia, normal levels of phosphate, and very high ALP. Vitamin D was in the range of insufficiency, and there was secondary hyperparathyroidism (Table-1). His urinary calcium and phosphate were low. Furthermore, the radiological skeletal survey showed a generalized decrease in bone density with a coarse trabecular pattern with several osteolytic lesions. To differentiate between types of VDDR, 1,25(OH)D was checked, which was very high, thus confirming the diagnosis of VDDR II.

**Table-1:** Various laboratory findings in the study cases.

| Variables | Normal Range | Case 1 | Case 2 |
|---|---|---|---|
| Corrected Calcium | 8.1-10.4 mg/dl | 5.34 | 6.82 |
| $sPO_4$ | 4.0-7.0 mg/dl | 3.6 | 2.01 |
| ALP | Up to 600 | 1120 | 1847 |
| Vitamin D | < 10 (D) 10-30 (I) | 23.5 | 74.9 |
| PTH | 7-53 pg/ml | 225 | 26.71 |
| Magnesium | 1.32-2.5 mg/dl | 1.33 | 1.32 |
| Urinary $PO_4$ | 340-1000 g/24 hrs | 0.1 | 503.5 |
| Urinary Calcium | 100-321 mg/24 hrs | <0.2 | 244.34 |
| Urine Volume | 800 to 2,000 ml/day | 3550 | 1900 |
| 1,25(OH)2D | 19.9 - 79.3 pg/ml | 150 | 130 |

ALP-Alkaline Phosphatase; sPO4-Serum Phosphate; PTH-Parathyroid Hormone; 1,25(OH)2D - 1,25-Dihydroxyvitamin D.
N-Normal, D-Deficiency, I-Insufficiency, ↓ - Low, ↑- High.

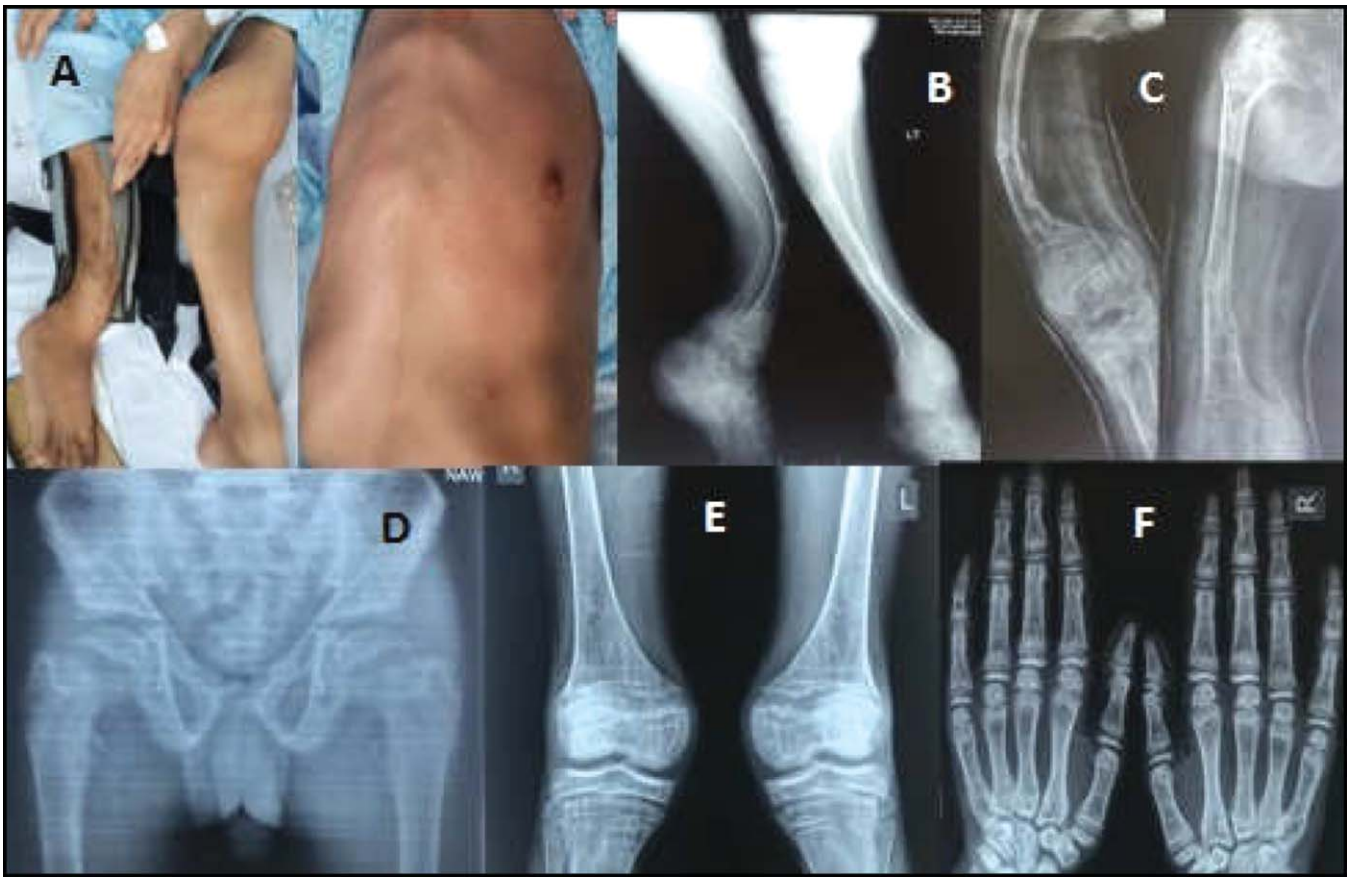


**Figure-1:** A) Bowing of legs, prominent chest and multiple bone deformities (Case 1). B & C) X-ray of legs showing multiple fractures, generalized osteopenia, and loser zones (Case 1). D, E & F) Radiological features of metabolic bone disease (Case 2).

**Case 2**

The second case was of a 15-year old male seen in Dec 2019 with complaints of pain in both legs since childhood and lately having difficulty in walking (Figure-1D-F). Skeletal survey was consistent with findings of metabolic bone disease; 1,25 (OH)D was very high, thus confirming the diagnosis of VDDR II. The clinical features were similar to case 1 and there was no history of any surgical correction of deformities.

Both patients were treated with high doses of vitamin D3 5000 IU/day, alphacalcidol 3 mcg/day, and calcium carbonate 3 g/day. Both patients showed significant improvement in symptoms as well as biochemical parameters.

Consent was obtained from the patient's guardian prior to the case publication. Confidentiality was maintained, and the patient's identity remained hidden.

## Discussion

Though there is a high prevalence of Vitamin D deficiency rickets,[3] the rare hereditary forms remain underdiagnosed. Both of our patients experienced skeletal deformities and growth retardation due to delayed diagnosis.

The children with VDDR II develop hypocalcaemia and severe rickets, usually within months after birth. Among other features or complaints are bone pain, muscle weakness, hypotonia, growth retardation, tooth cavities, and occasional convulsions.[4] Moreover, alopecia may be present at birth or develop within the first few months of life and progresses to alopecia totalis by childhood, which is generally irresponsive to the treatment.[5,6] The clinical presentation was identical in both the presented cases; difficulty in walking, multiple bone deformities, and growth retardation was seen, while alopecia was absent in both cases.

Clinical findings distinguishing VDDR II from VDDR I include markedly increased serum 1,25(OH)2D.[7] Both of our patients had similar laboratory findings; there was a significant decrease in the serum calcium, phosphate and an increase in the serum ALP levels. The level of 1,25(OH)2D was noticeably raised, and the 25(OH)D was

insufficient in case 1 and normal in case 2. Furthermore, case 1 had a high parathyroid hormone (PTH) level; he seemed severely affected and unstable than the other one with a normal PTH level (case 2).

It has been reported that up to 10 years post-puberty, there is a decrease in the requirement of calcium and vitamin D supplementation to maintain normal calcium and phosphate homeostasis. It coincides with a period of decreased bone growth, as well as a change in the fractional calcium absorption, which appears to be mediated by factors additional to vitamin D and PTH levels.

Both clinical and radiological improvements were observed among patients with HVDRR, when treated with pharmacological doses of vitamin D ranging from 5000 to 40,000 IU/d, 20 to 200 mg/d of 25(OH)D3, and 17 to 20 mg/d of 1,25(OH)2D3.[4] Some patients also respond to 1$\alpha$(OH)D3, while calcitriol treatment has also been described in different case reports.[8] When patients fail to respond to vitamin D or 1,25(OH)2D3, intensive calcium therapy is also used.[9] Our patients responded very well to the high doses of calcium, vitamin D, and alphacalcidiol. Clinical and biochemical improvement was evident within 3 months of treatment initiation.

## Conclusion

Both the presented cases had a tremendous delay in diagnosis that resulted in severe adverse skeletal deformities. Due to a lack of awareness regarding VDDR, most of the cases with this rare genetic condition remain undiagnosed for an extended period of time that ultimately causes severe outcomes in later stages.

**Disclaimer:** None to disclose.

**Conflict of Interest:** The authors declare no conflicts of interest.

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