

Case Report

Vitamin D - Dependent Rickets Type 2: A rare hereditary disorder with resistance to treatments

Anura Abeysundara^{1*}, Kuluni Wickramaratne², Shoba Jayakody³, PADAP Weerasinghe⁴, SDV Abeygunawardena⁵, DGH Warnasooriya⁶

¹Consultant Anaesthetist, Senior Lecturer - Faculty of Medicine, University of Peradeniya, Sri Lanka

^{2, 4, 5, 6}Temporary Lecturer, Faculty of Medicine, University of Peradeniya, Sri Lanka

³Senior House officer, Teaching Hospital, Kandy, Sri Lanka

*Corresponding author email: anuraabeysundara@gmail.com

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Abstract

Rickets is a skeletal disorder characterized by defective mineralization at the growth plate, resulting in bone deformities, growth retardation, and systemic complications. It may be calcipenic or phosphopenic, with acquired or hereditary etiologies. Nutritional rickets remains the most common worldwide, while hereditary forms are rare and diagnostically challenging. Vitamin D-dependent rickets (VDDR) is a hereditary subtype of calcipenic rickets. Among its forms, VDDR type 2 arises from mutations in the vitamin D receptor (VDR), resulting in end-organ resistance to calcitriol. We report a 19-year-old male diagnosed with VDDR type 2 at 18 months of age after delayed walking and florid rachitic features. Laboratory evaluation showed hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, and secondary hyperparathyroidism with radiological evidence of rickets. Standard doses of vitamin D and calcium produced no response. However, higher doses led to partial biochemical and clinical improvement. Despite therapy, the patient developed progressive skeletal deformities, osteoporosis, and multiple fractures requiring corrective orthopedic surgery. His younger sibling was later diagnosed with hereditary rickets, confirming a familial basis. This case highlights the diagnostic and therapeutic challenges of VDDR type 2. Recognition of poor response to

conventional therapy, coupled with biochemical and genetic evaluation, is essential for accurate diagnosis. Long-term multidisciplinary management, including orthopedic, endocrinological, and rehabilitative care, remains vital for improving outcomes in these rare hereditary rickets cases.

Key words

Calcipenic rickets, Hereditary rickets, Vitamin D-dependent rickets, Vitamin D receptor resistance.

Introduction

Rickets, historically known as the “English disease,” has been recognized for centuries as a cause of skeletal deformity in children. It arises from defective mineralization of the growth plate due to disturbances in calcium or phosphate homeostasis [1, 2]. The disorder remains clinically significant in both developed and developing countries.

Traditionally, rickets has been classified into calcipenic rickets and phosphopenic rickets based on biochemical abnormalities. Calcipenic rickets results from impaired calcium metabolism, most commonly due to vitamin D deficiency or defective vitamin D metabolism [1]. Phosphopenic rickets results from renal phosphate wasting or genetic defects in phosphate handling [2]. Recent evidence suggests phosphate deficiency may represent the common final pathway impairing chondrocyte differentiation [2].

Rickets may be acquired - due to nutritional deficiency, chronic illness, or drug-induced metabolic disturbance - or hereditary, resulting from genetic mutations affecting vitamin D or phosphate pathways [3, 4]. Nutritional rickets is the most prevalent globally, particularly in regions with limited sun exposure, inadequate dietary intake, or cultural practices restricting sunlight [2]. Hereditary forms, though rare, are diagnostically complex. The most common hereditary type is X-linked hypophosphatemic rickets, while vitamin D-dependent rickets (VDDR) remains relatively rare [4].

Vitamin D-dependent rickets (VDDR) includes several subtypes: Type 1A (renal 1α -hydroxylase

deficiency), Type 1B (hepatic 25-hydroxylase deficiency), Type 2 (VDR gene mutations), and Type 3 (increased catabolism of vitamin D metabolites) [3, 4, 5]. VDDR type 2 (VDDR2) is of particular clinical interest because of its marked treatment resistance. Despite adequate or elevated levels of calcitriol, tissues cannot respond due to defective or absent VDR function. This leads to persistent hypocalcemia, secondary hyperparathyroidism, and progressive skeletal deformity [3].

We report a rare case of VDDR type 2, presenting in childhood and followed over nearly two decades, illustrating the complexity of diagnosis and management, and emphasizing the need for integrative, long-term care.

Case report

A 19-year-old male presented to the emergency department following a motor traffic accident, sustaining a fracture of the right femur at the site of previous orthopedic fixation.

Early Development and Initial Diagnosis

The patient was born at term after an uneventful pregnancy and delivery. Maternal history was unremarkable. The mother had adequate nutritional supplementation and no history of anticonvulsant therapy. Developmental milestones were normal until 8 months of age. At this time, the patient exhibited growth faltering, failed to stand, and instead developed bottom-shuffling locomotion.

Despite nutritional counselling and supplementation, there was no improvement. By 18 months, he remained unable to stand. On examination, weight and height were below the

3rd percentile, while head circumference remained disproportionately large at the 97th percentile. Clinical signs included open anterior fontanelle, delayed dentition, caput quadratum, rachitic rosary, Harrison's sulcus, anterior bowing of legs, lumbar lordosis, swollen wrists, and protuberant abdomen. Alopecia was absent.

Laboratory and Radiological Findings

Investigations revealed hypocalcemia (serum calcium 1.6 mmol/L), hypophosphatemia, elevated alkaline phosphatase (>2000 IU/L), and markedly elevated parathyroid hormone. Liver and renal functions were normal. Tubular reabsorption of phosphate and maximum tubular reabsorption rate were normal, ruling out phosphopenic rickets. Radiographs demonstrated metaphyseal cupping, fraying, and generalized osteopenia.

Initial Management

He was started on intravenous ergocalciferol (10,000 IU/day for two weeks), followed by oral alfacalcidol (0.25 µg/day). However, there was no significant biochemical or clinical response. Doses were gradually escalated, after which partial improvement was noted, confirming suspicion of VDDR2.

Childhood and Adolescence

During early childhood, he experienced recurrent respiratory tract infections complicated by heart failure. At age 7, he developed genu valgum, later progressing to windswept deformity. DEXA scans demonstrated established osteoporosis. At age 17, he sustained a transverse fracture of the right femur, requiring corrective osteotomy and plating. Calcium and high-dose vitamin D supplementation were continued.

Current Presentation

At age 19, following a motor traffic accident, he sustained a repeat fracture of the right femur at the operative site. Radiographs confirmed refracture and replating was performed successfully. Family history subsequently revealed that his younger brother was also

diagnosed with rickets, suggesting a hereditary basis.

Image – 1: X-ray Imaging following right femur corrective osteotomy and plating at the age of 17 years (2022).



Image – 2: X- ray Imaging following the current road traffic accident (2024).



Discussion

Pathophysiology

Vitamin D is central to calcium-phosphate homeostasis. It undergoes hepatic hydroxylation to 25(OH)D, followed by renal hydroxylation to its active metabolite 1,25(OH)₂D. This active form binds to nuclear vitamin D receptors (VDRs) in target tissues, regulating gene expression involved in calcium absorption, phosphate metabolism, and bone mineralization [1, 3]. In VDDR2, mutations in the VDR gene impair binding of calcitriol to its receptor, resulting in end-organ resistance [3, 4, 5]. Despite high circulating calcitriol levels, downstream signalling fails, producing biochemical features of calcipenic rickets: hypocalcemia, hypophosphatemia (secondary to hyperparathyroidism), high ALP, and elevated PTH [1, 2].

Clinical Features

VDDR2 manifests early in life, often within the first year, with growth retardation, delayed motor milestones, rachitic deformities, and skeletal pain. Alopecia, when present, indicates a severe phenotype with absent receptor function [1, 4]. Extra-skeletal manifestations include muscle weakness, seizures, cardiomyopathy, recurrent respiratory infections, and anemia [2]. Our patient exhibited classical skeletal deformities, growth failure, osteoporosis, and repeated fractures, but alopecia was absent.

Biochemical Differentiation

Biochemical analysis distinguishes between VDDR subtypes (1): VDDR1A - Normal/elevated 25(OH)D, low 1,25(OH)₂D; VDDR1B - Low 25(OH)D, low 1,25(OH)₂D; VDDR2 - Normal/elevated 25(OH)D, elevated 1,25(OH)₂D; VDDR3 - Reduced both 25(OH)D and 1,25(OH)₂D due to accelerated degradation. Our patient's profile - elevated calcitriol, lack of response to conventional supplementation, and eventual partial improvement on high doses - was consistent with VDDR2.

Management Challenges

Management of VDDR2 is notoriously difficult. Standard therapy with vitamin D₂/D₃ or calcitriol often fails, necessitating very high doses of calcitriol and calcium to saturate defective receptors [5]. Patients with alopecia typically remain refractory and require long-term intravenous calcium infusion [3]. Regular biochemical monitoring is required to assess calcium, phosphate, ALP, and PTH, while renal ultrasound is essential to detect nephrocalcinosis secondary to high-dose therapy. Integrative management includes orthopedic interventions, physiotherapy, nutritional optimization, and genetic counselling [3, 4, 5].

Prognosis

Prognosis varies widely. Patients without alopecia often respond to high-dose regimens with improvement in growth and skeletal health. Those with alopecia tend to remain refractory and develop significant complications despite therapy [4, 5]. Early diagnosis and lifelong multidisciplinary management improve functional outcomes and quality of life.

Conclusion

VDDR2 is a rare hereditary form of rickets caused by VDR mutations, leading to end-organ resistance to calcitriol. It should be suspected in children with classical rickets unresponsive to conventional therapy. Diagnosis relies on biochemical testing and may be confirmed by genetic analysis. Treatment requires high-dose calcitriol and calcium, though responses vary. Long-term, multidisciplinary management including orthopedic, endocrinological, and rehabilitative approaches, is essential to minimize complications and optimize quality of life.

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