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Case Report

Vitamin D-dependent rickets: challenges in diagnosis and management

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ABSTRACT

Vitamin D-dependent rickets type II (VDDR-II) is a rare autosomal recessive disorder caused by mutations in the vitamin D receptor gene, leading to end-organ resistance to 1,25-dihydroxyvitamin D and poor response to conventional therapy. We report an adolescent female with genetically confirmed VDDR-II who presented with severe skeletal deformities, recurrent fractures, profound hypocalcaemia, secondary hyperparathyroidism, growth failure, and partial alopecia. Clinical, biochemical, radiological, and genetic evaluations confirmed the diagnosis. Despite intensive treatment with high-dose oral calcitriol and calcium supplementation, the patient required frequent intravenous calcium infusions to achieve partial biochemical stabilization, reflecting the resistant nature of the disease. Long-term follow-up demonstrated persistent growth impairment and fluctuating biochemical parameters closely related to treatment adherence. Notably, her sibling carrying the same vitamin D receptor mutation exhibited a significantly milder clinical phenotype, highlighting marked intrafamilial variability. This case illustrates the diagnostic and therapeutic challenges associated with VDDR-II and emphasizes the importance of early recognition, strict adherence to therapy, and multidisciplinary management to reduce complications and optimize outcomes.

Keywords: Vitamin D-dependent rickets type II, Vitamin D receptor mutation, Hypocalcaemia, Skeletal deformities, Alopecia

INTRODUCTION

Hereditary vitamin D-dependent rickets type II (VDDR-II) is a rare autosomal recessive disorder caused by mutations in the vitamin D receptor (VDR) gene, resulting in end-organ resistance to 1,25-dihydroxyvitamin D (calcitriol). Vitamin D plays a central role in calcium and phosphate homeostasis by promoting intestinal calcium absorption, modulating parathyroid hormone secretion, and supporting bone mineralization.[1] In VDDR-II, impaired VDR signalling leads to defective calcium absorption, hypocalcaemia, secondary hyperparathyroidism, and rickets despite normal or elevated circulating calcitriol levels.[2] The disease exhibits considerable clinical heterogeneity, ranging from mild biochemical abnormalities to severe skeletal deformities, fractures, and growth failure.[3] Severe forms often result from mutations in the DNA-binding domain of the VDR, leading to complete loss of function. Alopecia is a characteristic extra-skeletal manifestation in some patients and is often associated with more severe receptor dysfunction and treatment resistance.[4] Management of VDDR-II remains challenging, as conventional vitamin D supplementation is largely ineffective, frequently necessitating high-dose active vitamin D analogues and calcium supplementation, and in severe cases, intravenous calcium therapy. Therapeutic goals focus on partial biochemical correction, minimizing fractures, promoting linear growth and pubertal progression, and improving quality of life, while recognizing that complete normalization is rarely achieved. This report describes a severe case of VDDR-II, highlighting the clinical spectrum, intrafamilial variability, and long-term management challenges associated with this condition.

CASE REPORT

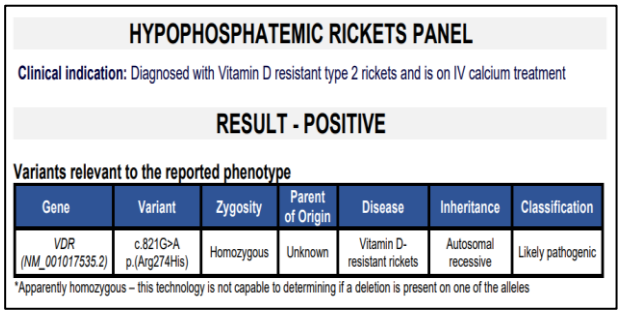
A 17-year-old female was diagnosed with hereditary vitamin D-dependent rickets type II (VDDR-II) in early childhood following evaluation for delayed growth, difficulty walking, and progressive musculoskeletal deformities. She was born full-term with no perinatal complications and had an unremarkable neonatal period. Symptoms became evident during early childhood, prompting further investigation.

Her clinical course was complicated by progressive skeletal deformities and bone fragility. She underwent bilateral knee epiphysiodesis for growth plate abnormalities and later sustained a displaced subtrochanteric femur fracture after minimal trauma, consistent with severe osteomalacia. At the time of current assessment, she required a wheelchair for mobility and had an unsteady gait with a high risk of falls.

Table 1: Highest and lowest laboratory values over 2 years in a patient with VDDR-II.

Parameter	Lowest value	Highest value	Reference range (units)
Calcium	1.62	3.19	2.08–2.65 mmol/l
Phosphate	0.49	1.04	0.78–1.65 mmol/l
Alkaline phosphatase	356	1940	46–116 u/l
Vitamin D (25-OH)	4.20	17.37	20 -40 ng/ml
Vitamin D (1,25)	>200	>200	19.9 – 79.3 pg/ml
Parathyroid hormone	9.30	45.10	1.96–9.33 pmol/l

Physical examination revealed classical rachitic deformities, including genu varum, bowing of the long bones, mild limb shortening, and restricted joint mobility. Partial alopecia involving the frontal scalp was noted at initial presentation, with gradual regrowth observed following treatment. No dental abnormalities were identified.



HYPOPHOSPHATEMIC RICKETS PANEL

Clinical indication: Diagnosed with Vitamin D resistant type 2 rickets and is on IV calcium treatment

RESULT - POSITIVE

Variants relevant to the reported phenotype

Gene	Variant	Zygosity	Parent of Origin	Disease	Inheritance	Classification
VDR (NM_001017535.2)	c.821G>A p.(Arg274His)	Homozygous	Unknown	Vitamin D-resistant rickets	Autosomal recessive	Likely pathogenic

*Apparently homozygous – this technology is not capable to determining if a deletion is present on one of the alleles

Figure 1: Summary of genetic testing results demonstrating a homozygous pathogenic variant (c.821G>A, p.Arg274His) in the vitamin D receptor (VDR) gene, confirming the diagnosis of hereditary vitamin D-dependent rickets type II.

Genetic testing confirmed a homozygous missense mutation c.821G>A (p.Arg274His) in the VDR gene, consistent with VDDR-II of autosomal recessive inheritance (Figure 1). Her younger brother, who carries the same vitamin D receptor (VDR) gene mutation, demonstrated a significantly milder phenotype and was able to ambulate independently, highlighting marked intrafamilial variability (Figure 2). Laboratory monitoring consistently demonstrated severe hypocalcaemia, hypophosphatemia, secondary hyperparathyroidism, and markedly elevated alkaline phosphatase levels, consistent with vitamin D-dependent rickets type II (VDDR-II). Serum calcidiol (25-hydroxyvitamin D) remained low despite supplementation, indicating impaired biological effectiveness, whereas calcitriol (1,25-dihydroxyvitamin D), the active form of vitamin D, was persistently elevated, reflecting end-organ resistance at the vitamin D receptor level. The patient's highest and lowest laboratory values recorded over a two-year follow-up period (2023–2025) are summarized in (Table 1).

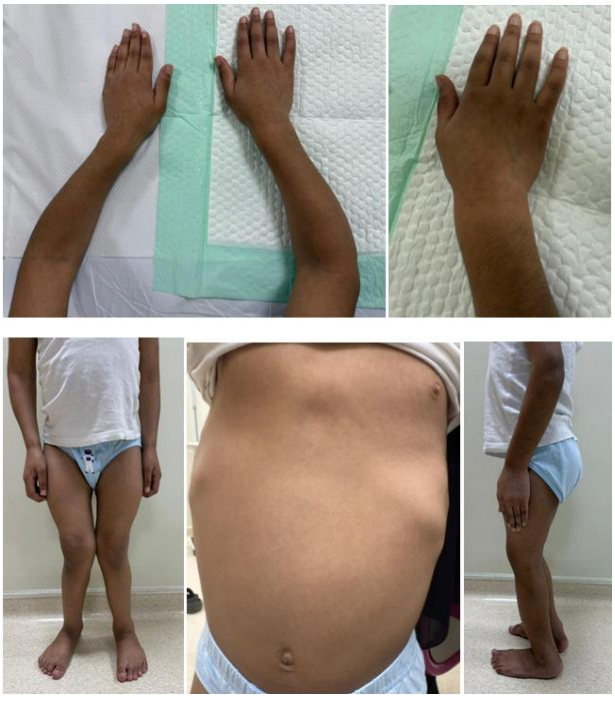


Figure 2: Clinical photographs of the patient's younger brother demonstrate the classical skeletal features of rickets, including a Harrison sulcus, bowing of the long bones, knock-knee deformity, and broadening of the wrists.

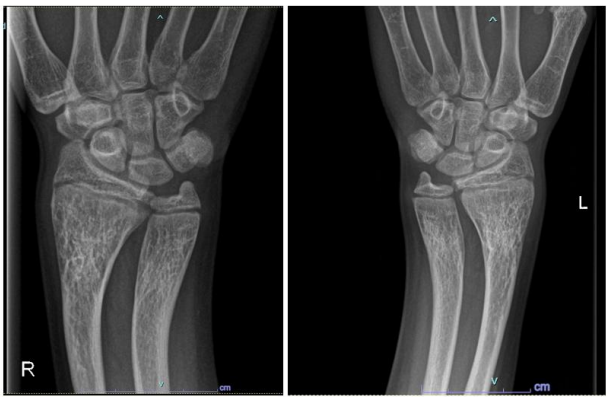


Figure 3: Wrist radiograph showing metaphyseal widening, cupping, and fraying of the distal radius and ulna consistent with active rickets.

Consistent with VDDR-II, the biochemical abnormalities showed only partial improvement with therapy, and complete normalization was never achieved due to persistent resistance to the vitamin D receptor. Fluctuations in these parameters were closely correlated with treatment compliance. During periods of more frequent follow-up in the summer months, when she attended clinic visits up to four times per week, calcium, phosphate, and alkaline phosphatase levels demonstrated the greatest improvement. Conversely, during intervals of less frequent attendance, her laboratory values deteriorated, highlighting the critical importance of consistent therapy and regular monitoring in the management of VDDR-II.

Table 2: LH and FSH levels (mid-cycle).

Hormone	Patient value	Reference range (mid-cycle peak)
LH	15.9 miu/ml	8.7- 76.3 miu/ml
FSH	3.42 muu/ml	3.4- 33.4 muu/ml

Skeletal surveys demonstrated reduced bone mineral density, metaphyseal widening and fraying, and bowing of the long bones. These radiographic findings were most prominent in the lower extremities and were consistent with chronic rickets-related deformities. Previous orthopaedic interventions were evident, including bilateral tibial fixation hardware from prior corrective procedures. No new acute fractures were identified at the time of evaluation. These imaging findings are characteristic of vitamin D-dependent rickets type II and reflect longstanding defects in bone mineralization (Figures 3–4). Longitudinal growth assessment revealed persistent failure to thrive despite prolonged therapy. Serial anthropometric measurements showed a body weight of approximately 31 kg and height persistently below the 3rd percentile for age and sex. Growth velocity remained suboptimal throughout follow-up, reflecting the chronic impact of impaired calcium homeostasis on skeletal development. These findings highlight the significant effect of VDDR-II on linear growth and overall somatic development (Figure 5).

Pubertal evaluation demonstrated Tanner stage 3 breast development, appropriate for mid-adolescence (Figure 6).

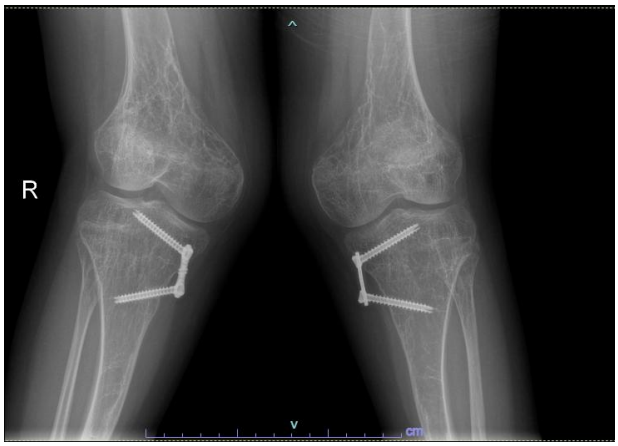


Figure 4: Bilateral knee X-rays reveal widened metaphyseal ends, bowing of the long bone shafts, and the presence of surgical fixation hardware in the tibial condyles from prior orthopaedic procedures.

Hormonal analysis revealed a luteinizing hormone (LH) level of 15.9 miu/ml and a follicle-stimulating hormone (FSH) level of 3.42 miu/ml, both within the normal mid-cycle reference range (LH: 8.7–76.3 miu/ml; FSH: 3.4–33.4 miu/ml) as her menstrual cycle approached the mid-cycle phase. These findings suggest preserved hypothalamic–pituitary–gonadal axis function despite chronic systemic illness (Table 2). The management of vitamin D-dependent rickets type II (VDDR-II) in this patient was directed toward normalization of serum calcium and phosphate levels, suppression of secondary hyperparathyroidism, promotion of skeletal mineralization, prevention of fractures, and support of normal growth and pubertal development. Owing to the underlying vitamin D receptor defect, the disease demonstrated resistance to conventional therapy, and biochemical targets were often difficult to achieve despite intensive supplementation. Irregular follow-up and inconsistent adherence further limited therapeutic effectiveness.

The patient received intermittent intravenous calcium therapy consisting of calcium gluconate 150 ml diluted with 150 ml of 5% dextrose, administered over six hours at a rate of 50 ml/hour via a port-a-cath. Continuous heart rate monitoring was performed during infusion, with temporary cessation of therapy if heart rate dropped below 80% of baseline, and resumption once hemodynamic stability was achieved. Oral therapy included alphacalcidol (1,25-dihydroxycalciferol) 4 mcg twice daily and calcium carbonate 1200 mg three times daily. Despite high-dose supplementation, complete biochemical normalization was not achieved due to persistent receptor resistance. Laboratory monitoring was conducted regularly. Prior to each weekly infusion, serum calcium, phosphate, alkaline phosphatase, creatinine, vitamin D, parathyroid hormone (PTH), and urine calcium-to-

creatinine ratio were assessed. Additionally, serum calcium, phosphate, alkaline phosphatase, and PTH were measured before daily infusions during intensive treatment periods.

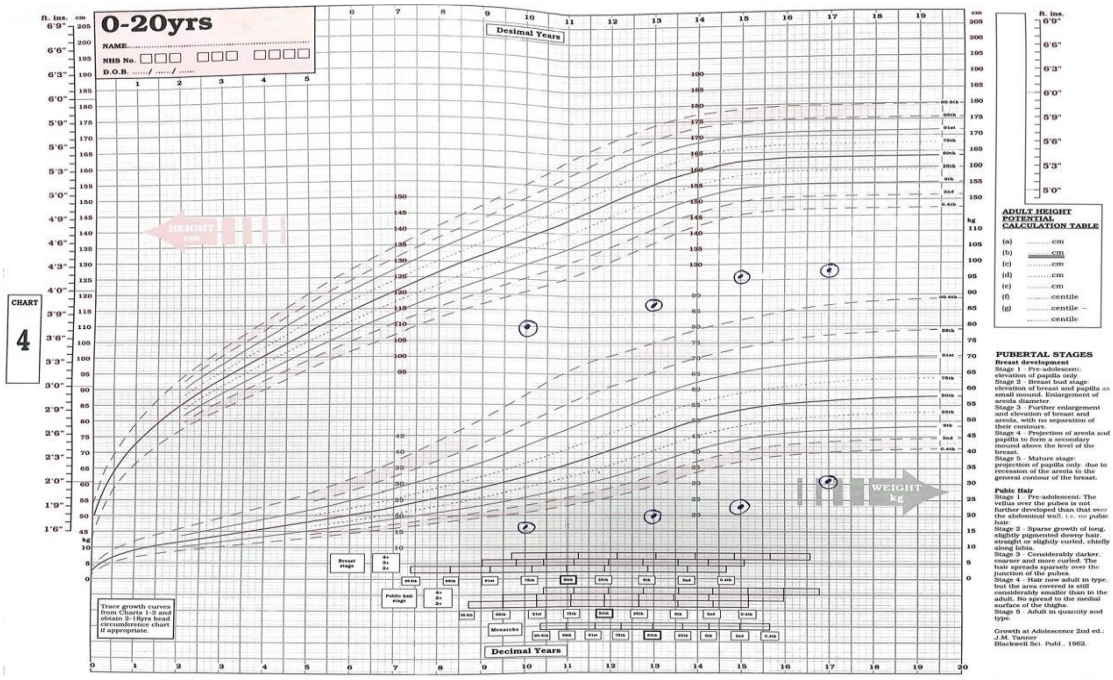


Figure 5: Growth chart illustrating the patient's height and weight plotted over time, highlighting persistent failure to thrive with measurements consistently below the 3rd percentile, indicative of chronic growth impairment associated with vitamin D-dependent rickets type II.

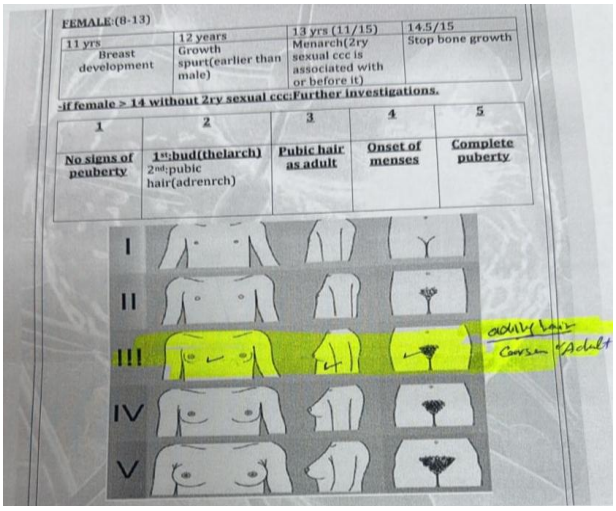


Figure 6: Pubertal assessment of the patient demonstrating Tanner stage 3 breast and pubic hair development, indicative of delayed pubertal progression in the context of VDDR-II.

Supportive care included paracetamol as needed for pain management and repeated counselling sessions emphasizing adherence to therapy and the importance of consistent biochemical and radiologic monitoring. Therapeutic goals were to maintain serum calcium within the normal range as consistently as possible, suppress secondary hyperparathyroidism, reduce bone turnover, and promote skeletal mineralization and linear growth. However, complete normalization was not anticipated given the underlying receptor resistance. Ensuring adherence to therapy and maintaining structured follow-up were considered essential to optimizing long-term outcomes.

DISCUSSION

Hereditary vitamin D-dependent rickets type II (VDDR-II) is a rare autosomal recessive condition characterized by severe rickets, hypocalcaemia, and secondary hyperparathyroidism despite elevated levels of circulating 1,25-dihydroxyvitamin D.[1] The pathogenesis is rooted in mutations within the vitamin D receptor (VDR) gene, which impair the receptor's ability to bind to the hormone or DNA, leading to profound end-organ resistance.[3] In this case, the patient's homozygous missense mutation c.821G>A(p.Arg274His) in the VDR gene directly correlates with this established molecular mechanism, representing a classic genetic cause of the disorder.[9]

Mutations in the VDR gene affect different functional domains of the receptor and contribute to phenotypic variability. DNA-binding domain mutations are frequently associated with severe disease and alopecia, whereas ligand-binding domain mutations produce milder skeletal manifestations without alopecia.[4,6–9] In our patient, the presence of alopecia, pronounced skeletal deformities, and persistent growth failure suggests a DNA-binding domain mutation, consistent with patterns described in prior

VDDR-II reports and cohort studies.[7-9] One of the most striking features of this case is the presence of partial alopecia. Alopecia in VDDR-II is a recognized clinical marker for severe receptor dysfunction and is frequently associated with resistance to conventional therapy.[2-5] While alopecia is often permanent in severe cases, some reports have shown varied responses to therapy.[8] In our patient, while alopecia was prominent at her initial presentation, some regrowth was observed following intensive treatment, aligning with literature suggesting that while alopecia is a marker of severity, its progression can be influenced by metabolic stabilization.[10] The intrafamilial variability observed between our patient and her younger brother, who shares the same VDR mutation but exhibits a significantly milder clinical phenotype, is a notable finding. Current reports on VDDR-II suggest that phenotype can vary even among patients with similar mutations, implying that additional genetic, epigenetic, or environmental factors may influence disease expression. Despite her younger brother's ability to ambulate independently, his presentation of skeletal features like the Harrison sulcus confirms that the underlying defect remains pathologically active.[4]

The management of VDDR-II remains a significant clinical challenge, often requiring a lifelong commitment to intensive therapy.[6] Unlike other forms of rickets, VDDR-II is largely unresponsive to standard vitamin D supplementation, often requiring massive doses of active vitamin D analogues and oral calcium.[1-4.] Our patient's reliance on intermittent intravenous calcium infusions through a port-a-cath highlights the severity of her receptor resistance. Furthermore, the close correlation between her biochemical fluctuations and clinical attendance proves the necessity of strict adherence and frequent monitoring, as seen in similar long-term retrospective studies.[6-9] Finally, the long-term impact on growth and skeletal integrity in this case was profound. The patient's persistent failure to thrive and history of subtrochanteric femur fractures demonstrate the devastating effect of chronic hypocalcaemia on skeletal development.[3.] Interestingly, despite these systemic challenges, her pubertal evaluation showed preserved hypothalamic–pituitary–gonadal axis function, suggesting that some endocrine systems may remain relatively resilient to the metabolic disturbances of VDDR-II despite the severity of the skeletal disease.[10]

CONCLUSION

Vitamin D-dependent rickets type II is a rare and clinically heterogeneous disorder associated with significant diagnostic and therapeutic challenges. Severe cases may demonstrate limited responsiveness to conventional therapy and require long-term intravenous calcium supplementation. This case highlights the importance of early genetic diagnosis, individualized therapeutic strategies, and lifelong monitoring to optimize growth outcomes and minimize the morbidity associated with chronic hypocalcaemia in patients with VDDR-II.

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