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Case Report

A tale of two cases: early diagnosis and variable outcomes in vitamin D-dependent rickets

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ABSTRACT

Vitamin D-dependent rickets (VDDR) is a rare inherited disorder of vitamin D metabolism or action, presenting with early-onset hypocalcemia, rickets, and growth failure. We report two contrasting cases of VDDR type I and type II that highlight important diagnostic and therapeutic differences. The first case, a female infant presenting with seizures, delayed milestones and limb deformities, showed hypocalcemia, elevated alkaline phosphatase, secondary hyperparathyroidism, and low 1,25-dihydroxyvitamin D levels; genetic testing confirmed a CYP27B1 mutation (VDDR-I), and treatment with oral calcium and calcitriol led to complete biochemical, radiological, and clinical recovery with near-normal growth. The second case, a male child from a consanguineous family with severe skeletal deformities, alopecia, and poor growth, demonstrated hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, markedly elevated alkaline phosphatase, normal 25-hydroxyvitamin D, and elevated 1,25-dihydroxyvitamin D levels; a vitamin D receptor (VDR) mutation confirmed VDDR-II, and despite aggressive therapy with high-dose calcium, active vitamin D, phosphate, and intermittent intravenous calcium, response remained suboptimal. These cases emphasize that early diagnosis and targeted therapy in VDDR-I can result in excellent outcomes, whereas VDDR-II is a severe, treatment-resistant condition, underscoring the critical role of detailed biochemical evaluation and genetic confirmation in children with refractory rickets.

Keywords: VDDR, Genetics, VDR

INTRODUCTION

Vitamin D-dependent rickets (VDDR) is a rare inherited disorder of bone mineralization caused by defects in vitamin D metabolism or action, leading to hypocalcemia, hypophosphatemia, and secondary hyperparathyroidism despite adequate vitamin D intake.[1] It is inherited predominantly in an autosomal recessive manner. VDDR is classified into two major types.[2] VDDR type I (VDDR-I) results from deficiency of the enzyme 1α-hydroxylase (CYP27B1), which is responsible for converting 25-hydroxyvitamin D into its active form, 1,25-dihydroxyvitamin D. VDDR type II (VDDR-II) is caused by resistance to 1,25-dihydroxyvitamin D due to mutations in the VDR.

Clinically, affected children usually present in infancy or early childhood with growth failure, hypotonia, delayed motor milestones, skeletal deformities, or hypocalcemic seizures.[3] Because of overlapping features with nutritional rickets, diagnosis is often delayed, leading to irreversible skeletal deformities.[4] We report two contrasting cases of VDDR-type I and type II-highlighting the importance of early diagnosis, genetic confirmation, and the variability in clinical outcomes.

CASE REPORT

Case 1

A 1-year-old female child, born in 2018 to non-consanguineous parents, presented at 6 months of age with recurrent seizures. She was born full term, delivered by LSCS with birth weight of 2.5 kgs, cried immediately after birth, and no history of NICU admission. Developmental history was suggestive of delayed motor milestones. She was initially treated as a case of epilepsy. On further evaluation, she was found to have widening of wrists, poor skeletal mineralization, and hip subluxation. There was no history of malabsorption or chronic illness.

Biochemical evaluation revealed hypocalcemia (S. calcium 7.8 mg/dl), elevated alkaline phosphatase (S. alkaline phosphatase>1000IU/L) and secondary hyperparathyroidism with inappropriately low normal levels of 1,25-dihydroxyvitamin D. MRI BRAIN was normal. EEG was suggestive of right parieto occipital spike and waves. Radiographs were suggestive of active rickets. A provisional diagnosis of vitamin D–dependent rickets type I was made. Genetic testing confirmed a pathogenic mutation in the CYP27B1 gene, consistent with VDDR-I.

She was treated with oral calcium supplementation and active vitamin D (calcitriol). Over follow-up, biochemical parameters gradually normalized, and radiological healing of rickets was observed. With sustained therapy, the child demonstrated significant clinical improvement, including correction of bony deformities, improved mobility, and catch-up growth over a period of two years. By 4.6 years of age, she had achieved near-normal growth parameters with complete resolution of rickets.

Table 1: Serial biochemical profile and growth parameters of case 1.

Age (in years)	Weight (in kg)	Height (in cm)	Sr. Ca (mg/dl) (8.8-10.2)	Sr. PO_4 (mg/dl) (2.4-5.1)	25 OH vit D (ng/ml) (>30)	1,25 dihydroxy vit D (pg/ml) (34.8-88.8)	PTH (pg/ml) (15-65)	ALP (iu/l), 15 days-<1 year: 122-469 1-10 years: 142-335
2	7.1	70	7.8		117.5			
2.2	7.4	70	6.51	2.79		33.8	572.7	
2.6	7.4	70	6.79	3.77	73.5		594.2	333
3.5	10.1	83	9.29	5.37				
3.10	11.4	87.5	10.3	5.9				301
4.6	11.7	90.7	9.0	3.3			481	

Table 2: Genetic analysis of case 1 (VDDR type I).

Gene (transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
CYP27B1(-) (ENST00000228606.9)	Exon 9	c.1357C>T (p.Arg453Cys)	Homozygous	VDDR, type I (OMIM#264700)	Autosomal recessive	Likely pathogenic (PM1,PM2,PP3,PP5)

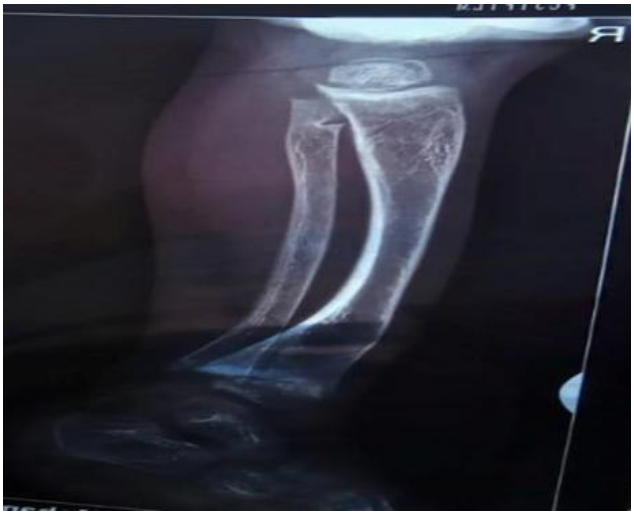

Figure 1: Radiograph of wrist at diagnosis in case 1 showing classical rachitic changes.

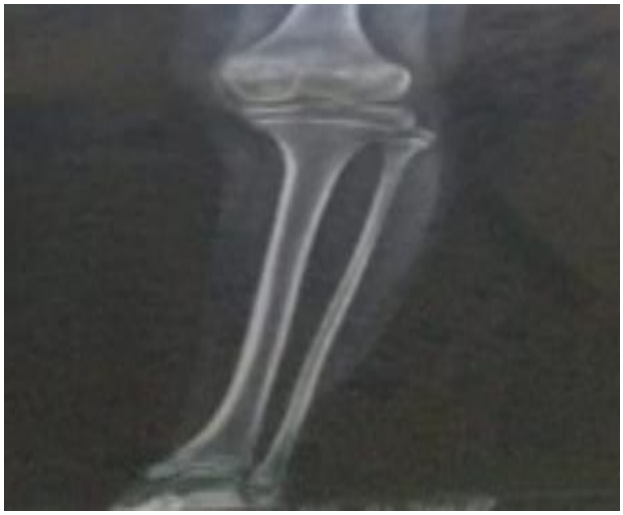

Figure 2: Radiographic healing after calcitriol therapy in case 1.

Case 2

A 3-month-old male child, the third offspring of a consanguineous marriage, presented with frontal bossing, with no evidence of other skeletal deformities, poor weight gain.

There was a significant family history of sibling deaths- 1st child girl expired at 4 years of age (seizure at 1 year of age, diagnosed with rickets at 1.5 years and alopecia, raising suspicion of VDDR type II). 2nd baby, LSCS at 7 months, mother had polyhydramnios, expired. Patient is 3rd baby, born full term, LSCS, birth weight: - 2.04 kgs, cried immediately after birth, no history of NICU stays. Early diagnosis could be made in this child due to previous sibling history. At 3 months of age, growth was appropriate for age, frontal bossing was evident on clinical examination and genitalia were normal male. Biochemical investigations showed Sr. calcium-7.68 mg/dl, Sr. phosphorous: -2.6 mg/dl, markedly elevated alkaline phosphatase -1647 IU/l, and normal 25-hydroxyvitamin D levels, with elevated parathyroid hormone levels. Levels of 1,25-dihydroxyvitamin D were elevated, suggestive of end-organ resistance. Genetic analysis confirmed a mutation in the VDR gene, consistent with VDDR type II.

The child was managed with high-dose oral calcium supplementation, alfacalcidol, calcitriol, and phosphate supplements. Despite aggressive medical management, metabolic control remained difficult, and skeletal deformities showed limited improvement. The child required intermittent intravenous calcium therapy to maintain normocalcemia. Growth response remained suboptimal, highlighting the severe and treatment-resistant nature of VDDR-II.

Table 3: Serial biochemical profile and growth parameters of case 2.

Age (in years)	Height (in cm)	Weight (in kg)	Sr. Ca (mg/dl)	Sr. PO_4 (mg/dl)	25 OH vit D (ng/ml)	1,25 dihydroxy vit D (pg/ml)	PTH (pg/ml)	ALl (iu/L)
3.8	76	8.5	6.9	3.2				1903
4.5	79	9	8.6	2.8				1323
5	82	10	8.3	2.6				1159
5.10	87	10.5	7.7	2.9			534	1149
6.9	90.5	12	7.2	2.9	28.7	33.4		1255
7.4	92.4	12.8	6.3	3.2			500.20	843
8								

Table 4: Genetic analysis of case 2 (VDDR type II).

Gene (transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
VDR (-) (ENST00000550325.1)	Exon 7	c.872T>A (p.Val291Asp)	Homozygous	VDDR, type 2A	Autosomal recessive	Likely pathogenic

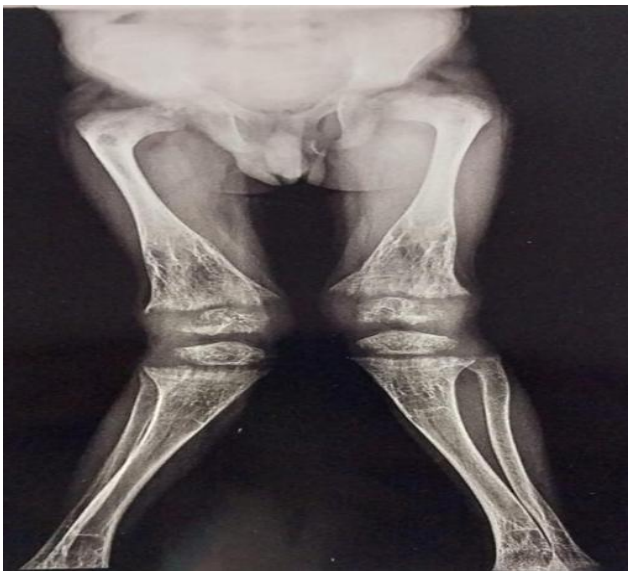

Figure 3: Lower limb radiograph in case 2 demonstrating severe metaphyseal widening and deformity.

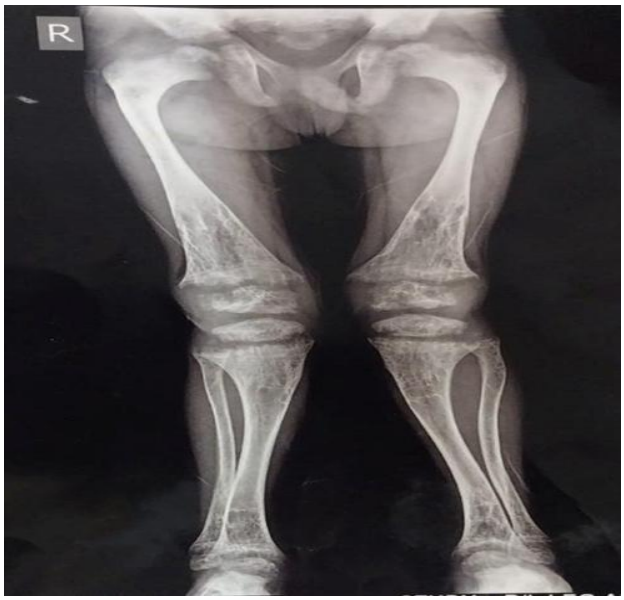

Figure 4: Follow-up radiograph after treatment showing partial healing in case 2.

DISCUSSION

VDDR comprises a rare group of inherited disorders characterized by impaired vitamin D metabolism or end-organ resistance, resulting in defective calcium homeostasis, hypophosphatemia, secondary hyperparathyroidism, and impaired skeletal mineralization. Although the clinical manifestations resemble nutritional rickets, the underlying molecular defects necessitate fundamentally different therapeutic approaches. The present report highlights two genetically confirmed cases of VDDR-type I and II-with markedly different clinical presentations and outcomes, emphasizing the importance of early biochemical evaluation, molecular diagnosis, and individualized management.

The first patient had classical features of VDDR type I caused by a homozygous CYP27B1 mutation, presenting with hypocalcemic seizures, delayed motor milestones, skeletal deformities, and radiological evidence of active rickets. Deficiency of renal 1α-hydroxylase results in impaired conversion of 25-hydroxyvitamin D to the biologically active metabolite, 1,25-dihydroxyvitamin D, leading to reduced intestinal calcium absorption and secondary hyperparathyroidism. Similar clinical presentations have been reported by Levine et al who described hypocalcemic seizures and growth failure as common initial manifestations of VDDR-I in infancy.[1] Likewise, Haffner et al emphasized that persistent rickets associated with low or inappropriately normal 1,25-dihydroxyvitamin D concentrations despite adequate vitamin D stores should prompt evaluation for CYP27B1 deficiency.[4] In our patient, prompt initiation of calcitriol and oral calcium supplementation resulted in normalization of biochemical parameters, radiological healing, correction of skeletal deformities, and near-normal growth, consistent with the excellent prognosis reported in previous studies when treatment is instituted early.

In contrast, the second patient demonstrated the characteristic phenotype of VDDR type II caused by a homozygous VDR mutation. Despite early diagnosis because of a significant family history, the child developed persistent hypocalcemia, severe biochemical abnormalities, progressive skeletal deformities, and required prolonged treatment with high-dose calcium, calcitriol, alfacalcidol, phosphate supplementation, and intermittent intravenous calcium. The elevated circulating concentration of 1,25-dihydroxyvitamin D observed in this patient reflects preserved hormone synthesis but impaired receptor-mediated biological action. Resistance at the VDR level prevents effective intestinal calcium absorption and bone mineralization despite adequate active vitamin D levels. Similar biochemical findings have been consistently reported in hereditary vitamin D-resistant rickets, where elevated 1,25-dihydroxyvitamin D serves as an important diagnostic clue distinguishing VDDR-II from VDDR-I and nutritional rickets.

Our findings closely resemble those reported by Vupperla et al who described a child with VDDR-II presenting with alopecia, hypocalcemia, markedly elevated alkaline phosphatase, and poor response to conventional vitamin D therapy.[5] The authors emphasized that VDDR-II should be suspected whenever rachitic changes fail to improve despite adequate vitamin D supplementation. Likewise, Takeda et al reported two siblings with hereditary vitamin D-resistant rickets associated with alopecia who required prolonged treatment with very high doses of vitamin D and calcium before achieving biochemical remission.[6] Although some patients eventually demonstrate improvement following prolonged intensive therapy, skeletal deformities and growth impairment frequently persist. Similar to these observations, our patient continued to show suboptimal growth and incomplete skeletal recovery despite aggressive medical management, illustrating the refractory nature of VDDR-II.[7,8]

The contrasting outcomes observed in these two cases underscore the fundamental pathophysiological differences between VDDR-I and VDDR-II. In VDDR-I, replacement of the deficient active vitamin D metabolite effectively bypasses the enzymatic defect, resulting in rapid normalization of calcium metabolism and healing of rickets. Conversely, in VDDR-II, the underlying defect lies within the VDR itself; therefore, administration of active vitamin D alone cannot adequately overcome receptor resistance. Consequently, treatment often requires prolonged administration of supraphysiological doses of calcium, active vitamin D analogues, phosphate supplementation, and occasionally intravenous calcium infusions to maintain normocalcemia. Even with intensive therapy, clinical outcomes remain variable and are generally less favorable than those observed in VDDR-I.

These cases also highlight the critical value of molecular genetic testing. Although biochemical findings strongly suggested the diagnosis in both patients, identification of pathogenic CYP27B1 and VDR mutations established the precise subtype, enabled appropriate therapeutic planning, and facilitated genetic counselling for the families. This is particularly important in populations where consanguineous marriages are common, as autosomal recessive inheritance substantially increases recurrence risk. Early genetic confirmation also permits prenatal counselling and early screening of siblings, thereby preventing delayed diagnosis and irreversible skeletal complications.[9,10]

Another important clinical message from these cases is the need to distinguish inherited forms of rickets from nutritional vitamin D deficiency. Nutritional rickets usually responds rapidly to vitamin D replacement, whereas persistent hypocalcemia, recurrent seizures, family history of affected siblings, parental consanguinity, alopecia, or failure to respond to conventional vitamin D therapy should raise suspicion for

VDDR. Comprehensive biochemical evaluation-including serum calcium, phosphate, alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D-combined with targeted molecular testing enables early and accurate diagnosis. Such an approach minimizes unnecessary investigations, prevents inappropriate treatment, and significantly improves long-term outcomes.

In conclusion, our two genetically confirmed cases illustrate the broad phenotypic spectrum of VDDR. The excellent clinical recovery achieved in the child with VDDR-I following early calcitriol therapy contrasts sharply with the persistent treatment resistance observed in VDDR-II despite intensive management. These findings are consistent with previously published literature and reinforce the importance of early recognition, comprehensive biochemical assessment, molecular confirmation, and multidisciplinary follow-up. Increased awareness among pediatricians regarding these rare inherited disorders is essential for timely diagnosis, optimized treatment, prevention of irreversible skeletal deformities, and appropriate genetic counselling for affected families.

CONCLUSION

VDDR represents a heterogeneous group of genetic disorders with overlapping clinical features but distinct therapeutic responses. Early diagnosis with detailed biochemical evaluation and genetic confirmation is crucial for optimal management. While VDDR-I has an excellent prognosis with timely treatment, VDDR-II remains challenging with limited growth and skeletal outcomes despite aggressive therapy. Increased awareness and early intervention can significantly improve quality of life and long-term outcomes in affected children.

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