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Case Report

An unusual presentation of vitamin D dependent rickets type 2 with low 25 (OH) D_3 levels and alopecia: a case report of two siblings

Monisha Ramesh*, Vivek Chopra, Neeraj Dhawan, Sadbhavna Pandit

Department of Pediatrics, Government Multispeciality Hospital, Sector-16, Chandigarh, Punjab, India

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***Correspondence:**
Dr. Monisha Ramesh,
E-mail: rsmonu.anju@gmail.com

ABSTRACT

Vitamin D-dependent rickets type 2 (VDDR2) is a rare autosomal recessive (AR) disorder caused either by a mutation in the Vitamin D receptor gene or overexpression of the binding protein leading to end-organ resistance to 1,25 $(OH)_2$ vitamin D3 or defective hormonal actions respectively. It clinically represents growth retardation presenting in the 1st year of life and is frequently associated with alopecia totalis and markedly elevated levels of 1, 25$(OH)_2$ D, which differentiates it from VDDR type 1. We hereby report siblings of a family, who presented with clinical, radiological features of rickets and alopecia totalis. To our knowledge, only a few cases have been reported in literature describing the AR-pattern and low 25(OH)D3 levels in VDDR2.

Keywords: Vitamin-D dependent rickets type 2, Alopecia, 1, 25-dihydroxy vitamin D3

INTRODUCTION

Rickets, a metabolic bone disorder, develops due to decreased mineralization of the growth plate due to defective metabolism or functions of calcium or phosphate and/or deficiency of vitamin D or decreased activity of alkaline phosphatase.[1] It is broadly classified into calciopenic (defect in metabolism or functions of calcium/deficiency of vitamin D) or phosphopenic (renal phosphate wasting).

Genetic causes of rickets (hereditary rickets), account for about 13% including disorders of vitamin D biosynthesis and action such as vitamin D-dependent rickets type 1A (VDDR1A), type 1B (VDDR1B), type 2A (VDDR2A) and type 2B (VDDR2B).[2] VDDR2 is also known as pseudovitamin D-deficiency type 2, hypocalcemic vitamin D-resistant rickets or rickets-alopecia syndrome.[3] Inactivating homozygous or compound heterozygous mutations of the gene chromosome 12q12-q14, encoding the vitamin D receptor VDR (MIM#601769), results in VDDR type 2A.[2] VDDR2B appears to result from overexpression of a hormone response element-binding protein that interferes with the actions of 1,25 $(OH)_2$ D.[4] VDDR type II causes rachitic changes that are not responsive to vitamin D treatment. Alopecia is more commonly associated with severe cases of type IIA than IIB.

The first case reported in 1978 by Brooks et al was a 22-year-old woman with hypocalcemia, secondary hyperparathyroidism, osteomalacia and osteitis fibrosa cystica with normal serum 25-hydroxyvitamin D and markedly increased serum 1, 25 (OH) D.[5] They named it VDDR type II and mutations in VDR gene was found to be causative in 1988.

CASE REPORT

Two siblings, an 8 years girl and 2 years 3 months boy, born to non-consanguinous parents had similar complaints of inability/difficulty to walk and loss of hair over the scalp. Both the siblings were born full-term after an uneventful pregnancy. They were healthy at birth. By

2-3 months of life, both had loss of hair over the scalp and had a significant delay in the attainment of motor milestones like standing and walking. Although other domains of development were attained normally. Both were on prophylactic vitamin D supplementation since birth and were started on complementary feeds at around 8 months of age. Gradually the elder girl developed a bony deformity of both lower limbs due to which her ability to stand is now only with assistance, limiting her mobility and daily activities. The boy was hardly able to stand with support yet. There was no history of delayed dentition. Neither did they have any history of previous hospitalization nor any history and signs suggestive of malabsorption, other vitamin deficiencies, or other systemic illness. They had another male sibling of 5 years, who was absolutely normal. The pedigree chart of the family is illustrated in Figure 1.

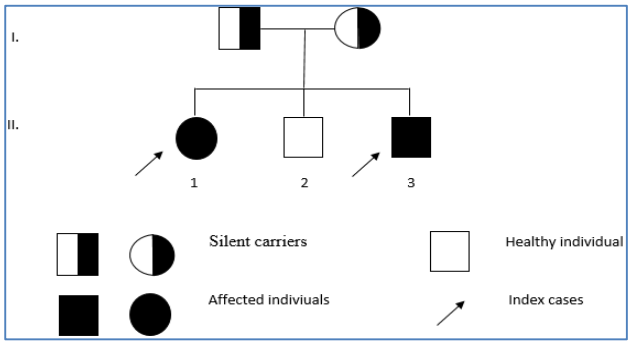

Figure 1: Pedigree of the family.

The 8 years old elder girl (1st case) had weight and length less than 3rd centile, normal head circumference for age, and disproportionate short stature. She had alopecia totalis with a complete absence of eyebrows and body hair with very few eyelashes. She also had frank signs of florid rickets like frontal bossing, dental caries, Harrison's sulcus, palpable rachitic rosary, kyphoscoliosis, potbelly, widening of wrist and ankle with saber tibia and talipus varus of the left ankle. Clinical images of this case are shown in the Figures 2 and 3.

Features of rickets were confirmed radiographically with X-ray of wrist and knee joints which showed widening of epiphysis and metaphysis, fraying at metaphyseal ends, decreased mineralization, and trabeculations of diaphysis with thinned out cortex of long bones and anterior bowing of left femur. Radiological images are depicted in Figure 4.

Our 2nd case, her youngest sibling (2 years 3 months old boy), had weight and length below the 1st centile, head circumference was between 3rd and 50th centile, and had proportionate short stature. Alopecia with few strands (15-20) of terminal hair, complete absence of eyebrows and body hair with very less eyelashes, frontal bossing with closed anterior fontanelle, dental caries, Harrison's sulcus, rachitic rosary, kyphosis, widening of the wrist and double malleoli were present. Radiographically he had widening of the growth plate, fraying and splaying at metaphyseal ends of distal radius and ulna with marked osteopenia. Clinical presentation and radiological findings of this case are shown in Figures 5-7.

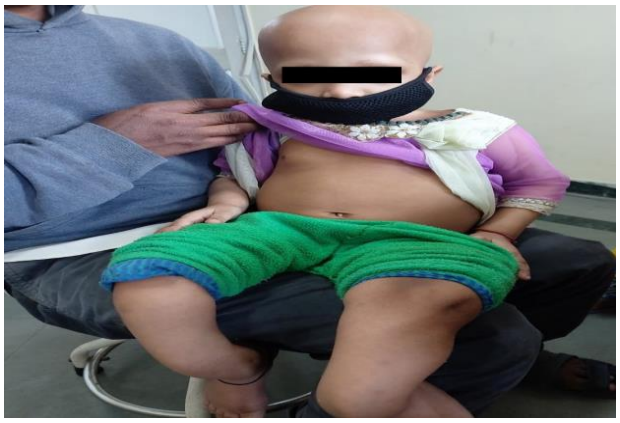

Figure 2: 8-year-old girl with alopecia totalis, potbelly and saber tibia.

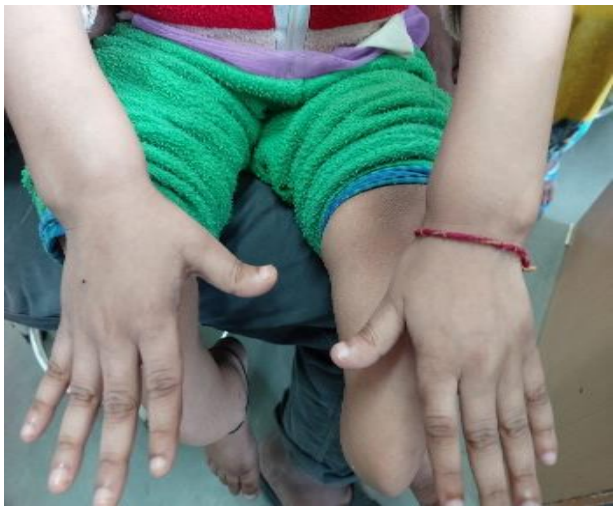

Figure 3: Widening of bilateral wrist of the first sibling.

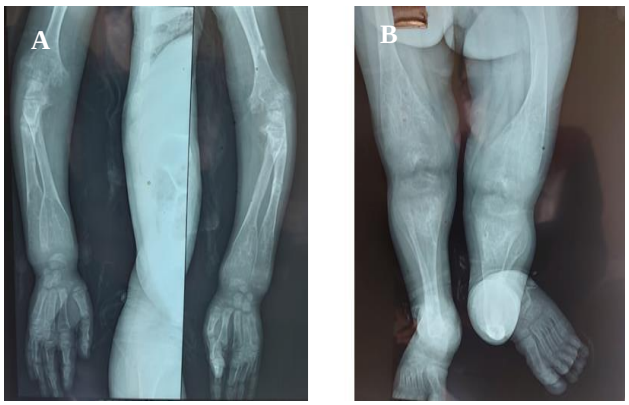

Figure 4 (A and B): X-ray of bilateral upper and lower limbs of 1st case.

Figure 5: 2nd case with alopecia and few strands of terminal hair.

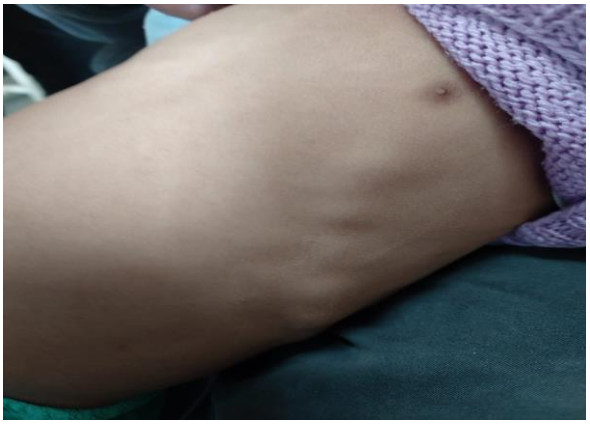

Figure 6: Rachitic rosary and Harrison's sulcus of 2nd case.

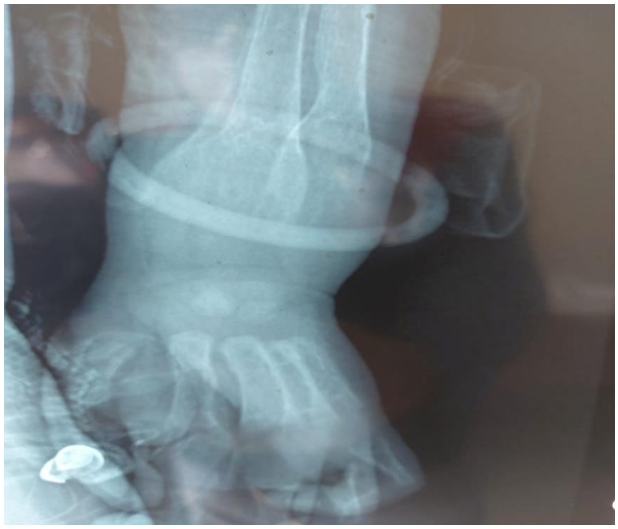

Figure 7: X-ray of left wrist joint of 2nd case.

Blood investigations of both siblings revealed dimorphic anemia with eosinophilia. Serum electrolytes and renal function tests were within normal limits. They had reduced levels of serum calcium, phosphorus, and 25(OH)D3 levels. Serum ALP, parathormone, $1,25(OH)_2D3$, and urine phosphorus levels were highly elevated. Laboratory parameters are enumerated in Table 1.

Based on these clinical, biochemical, radiological features and the presence of extremely high circulating levels of $1,25(OH)_2D3$ with alopecia, both of these siblings were diagnosed as VDDR type 2. They were started on 3 months trial of high-dose vitamin D (2 µg/day of 1,25-D) and oral calcium (1000 mg/day). Genetic testing for the identification of the type of mutation/protein overexpression was not possible due to financial constraints.

Table 1: Metabolic profile of both the cases included in the study.

Investigation	1st case	2nd case	Normal range[6]
Serum calcium (mg/dl)	6.7	8.5	8.8-10.8
Serum phosphorus (mg/dl)	3.09	2.09	3.2-5.8
Serum alkaline phosphatase (U/l)	7216	5128	100-320
Serum parathormone (pg/ml)	232	449	15-65
25(OH)D3 (ng/ml)	6.25	4.52	20-100
$1,25(OH)_2D3$ (pg/ml)	>200	>200	16-65
Urine phosphorus (mg/dl)	55	50.2	<3.4
Urine calcium (mg/kg/day)	Nil	0.21	<4

DISCUSSION

Vitamin D absorbed from the skin and intestine is hydroxylated to 25-hydroxyvitamin D3 (25-OHD3) in the liver. Later, it is transported to the kidney, through a binding protein, where it undergoes hydroxylation forming an active metabolite, 1,25-dihydroxyvitamin D3 (1, 25 $(OH)_2$ D3). The tissue receptors for vitamin D metabolites are localized in the kidney, intestine, pancreas, parathyroid gland, muscle, pituitary, skin, and bones, and 1, 25 $(OH)_2$ D3 binds specifically to a receptor in the nuclei to stimulate calcium transport and also controls the expression of target genes mediated through the nuclear VDR.[7] VDR, a 50-kDa protein, belongs to the steroid-thyroid-retinoic acid receptor superfamily of genes, comprising of at least two functional domains: a

steroid hormone-binding domain and a DNA-binding domain.[8] The most common genetic abnormality was a point mutation within the steroid-binding domain with the second type being abnormality in a zinc-finger region of the DNA-binding domain, which was confirmed in two families.[9]

The protein by-products formed during the mutation of the VDR gene disrupt the hair cycle leading to alopecia.[7] The absence of ligand-independent function of the VDR in keratinocytes, required for anagen initiation, is hypothesized to be the reason for alopecia. Also, the close linkage between VDR with retinoid X receptor may be critical for normal differentiation of the follicular epithelium and dermal papillae into the various components required for normal cycling. Alopecia usually starts at birth and ends in childhood. The extent of alopecia ranges from decreased hair on the body parts including eyebrows, eyelashes, and body hair (alopecia areata/partial alopecia) to complete hair loss over the body (alopecia totalis/complete alopecia).[10] The development of alopecia is felt to be associated with more profound 1, 25 $(OH)_2$ D3 resistance.[11]

Due to its rarity and delay in diagnosis and treatment, VDDR II results in deformities of lower limbs, severe growth retardation, acidotic breathing, cataracts, alopecia, and the presence of a dental abscess.[12] There was elevated alkaline phosphatase and low serum phosphorus levels. The diagnostic hallmark was increased serum levels of 1, 25 $(OH)_2$ D3. The mutations alter the absorption of calcium and phosphate resulting in hypocalcemia and hypophosphatemia.

A few rare case reports of VDDR II published includes, a 24-year-old woman who was reported with a late presentation, showing improvement in rickets after adequate treatment.[3] Mehmedali Azemi et al, worked on the first case of VDDR II in Kosovo, a 25 months old girl, who presented with convulsions and was treated accordingly.[12] Kruse et al. reported healing of rickets in two siblings affected by VDDR II with total alopecia following prolonged courses of high-dose vitamin D but the alopecia did not improve even after years of vitamin D therapy.[13,14] Whereas work of Inamdar PR and Smita Mishra et al reported alopecia responding to 1,25 $(OH)_2$D3.[12] Also, Takeda et al., showed improvement in two siblings with VDDR type II associated with alopecia whose treatment included 50,000 IU of vitamin D2 for 2 years, and no recurrence was observed 14 years after cessation of therapy.[15]

Hardly any of these cases had low levels of 25(OH)D3 which was consistent in both of our cases. They were diagnosed to have VDDR2 as they had highly elevated levels of 1,25-D, frank clinical and radiological features of rickets with alopecia. Their other sibling was completely normal which again reinforced the inheritance pattern.

CONCLUSION

Management of the VDDR2 includes administering high doses of oral calcitriol (1-6 µg/kg/day in two divided doses) and supplemental calcium (1-3 g/day) for mild to moderate cases. In severe cases, high doses of intravenous calcium infusion give a good response, but long-term administration results in complications such as cardiac arrhythmia, hypercalciuria, nephrocalcinosis, catheter-related sepsis, and extravasation of calcium.

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