Case Report

Familial Vitamin D-dependent rickets Type 2A: A report of two cases with alopecia and oral manifestations

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Abstract

Rickets is a metabolic bone disease that develops as a result of inadequate mineralization of growing bone due to disruption of calcium, phosphorus and/or Vitamin D metabolism. In addition, several rare genetic causes of rickets have also been described, which can be divided into two groups. The first group consists of genetic disorders of Vitamin D biosynthesis and action, such as Vitamin D-dependent rickets Type 1A, Type 1B, Type 2A (VDDR2A) and Type 2B. The second group involves genetic disorders of excessive renal phosphate loss (hereditary hypophosphatemic rickets). VDDR2A is a rare autosomal recessive disorder caused by mutation in the Vitamin D receptor gene, leading to end-organ resistance to $1,25(OH)_2$ Vitamin D_3. It clinically represents growth retardation presenting in the 1st year of life and frequently associated with alopecia totalis, which differentiates it from VDDR Type 1. Due to target organ resistance, its response to Vitamin D is poor. We report two cases of familial VDDR2A, with alopecia and oral manifestations.

Keywords: Alopecia, calcium, rickets, Vitamin D

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INTRODUCTION

Rickets is a metabolic bone disorder that develops as a result of decreased mineralization of the growth plate in the growing infant, child and adults due to defect in metabolism or functions of calcium or phosphate and/or deficiency of Vitamin D or decreased activity of alkaline phosphatase.[1,2] Rickets is classified into various types, but broadly classified based on common etiological factors into two types as calciopenic (defect in metabolism or functions of calcium/deficiency of Vitamin D) or phosphopenic (renal phosphate wasting).[2,3]

In addition, genetic causes of rickets (hereditary rickets) are rare, accounting for about 13% of total rickets.[4] They are classified into two groups. The first group consists of genetic 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). Inactivating homozygous or compound heterozygous mutations of VDR (MIM#601769), the gene encoding the Vitamin D receptor called Vitamin D-resistant rickets or VDDR Type 2A is an autosomal recessive disorder.[5] The second group involves genetic disorders of excessive renal phosphate loss (hereditary hypophosphatemic rickets).[6,7] Here, we report such rare cases of familial VDDR2A, with alopecia and oral manifestations.

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CASE REPORTS

Case 1

A 14-year-old male reported to the department with a history of delayed milestones, abnormal movement of head for 2 months and abnormality of knee joint since birth [Figure 1a]. However, he progressively developed marked weakness, gait abnormality, easy fatigability and cramps. He was a product of consanguineous marriage with delayed milestones and delayed teeth eruption. Medical history revealed jaundice immediately after birth and tonsillectomy at the age of 5 years. No abnormality was detected on systemic examination of cardiovascular, respiratory and central nervous system.

Clinical examination revealed sparse eyebrows, drooping of the shoulders and slight deformity of knees with bowing of legs. It also revealed stable vitals, height of 142 cm and weight of 35 kg. Features of stiffening of fingers with severe hypocalcemia (Chvostek's sign and carpopedal spasms) were positive. Alopecia was observed and gives history since birth [Figure 1b].

Intraoral examination revealed normal mouth opening with competent lips, enamel hypoplasia, dentin defects, dental caries in relation to 36, 37 and erupting 13 [Figure 2]. An orthopantomogram [Figures 3 and 4] revealed generalized severe enamel hypoplasia, dentin abnormalities, dental caries in relation to 36, 37, erupting 13 and impacted supernumerary teeth in relation to 35, 36 and 45, 46 with enlarged pulp chambers.

Baseline investigations were within normal limit. Severe hypocalcemia (serum calcium: 6.3 mg/dL) and hypophosphataemia (2.1 mg/dL) as well as markedly raised alkaline phosphatase and parathormone levels were observed. Skeletal survey did not reveal features of rickets or osteomalacia. Evaluation for renal tubular acidosis and hypophosphatemic rickets was negative. Levels of Vitamin D metabolites disclosed normal 25-hydroxyvitamin D; however, marked increase in 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) was noted. In our case, the onset of disease at 14 years of age was the absence of response to routine doses of calcium supplements, and the characteristic laboratory abnormalities were compatible with the diagnosis of VDDR2A.

Based on the patient's history, clinical examination and laboratory findings, it is diagnosed as VDDR2. Further, the patient was referred to DNA test which revealed homogeneous missense variation in exon-10 of the VDR gene (chr123:48238786) that results in the

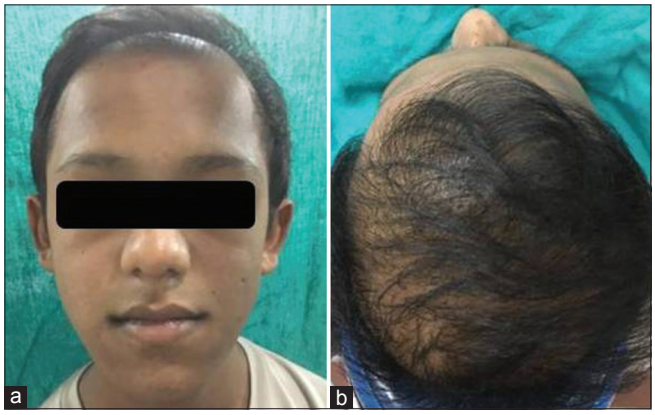

Figure 1: (a and b) Profile picture with sparse hair

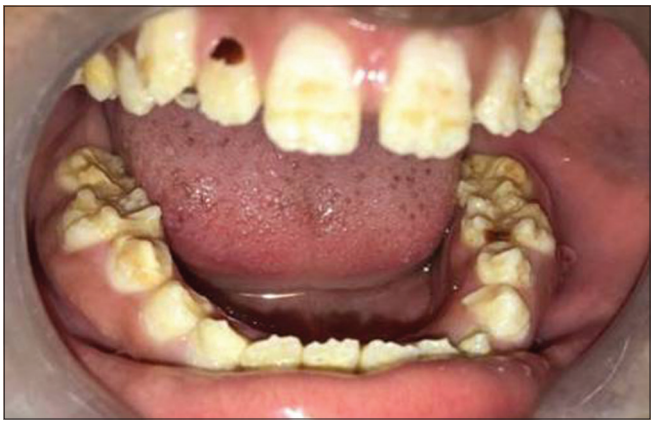

Figure 2: Intraoral examination revealed enamel hypoplasia and dentin defects with dental caries

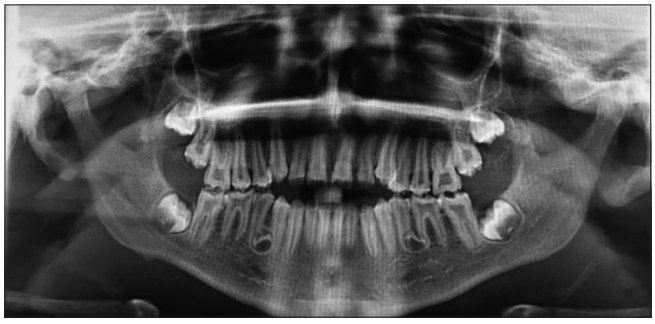

Figure 3: An orthopantomogram revealed generalized severe enamel hypoplasia, dentin abnormalities

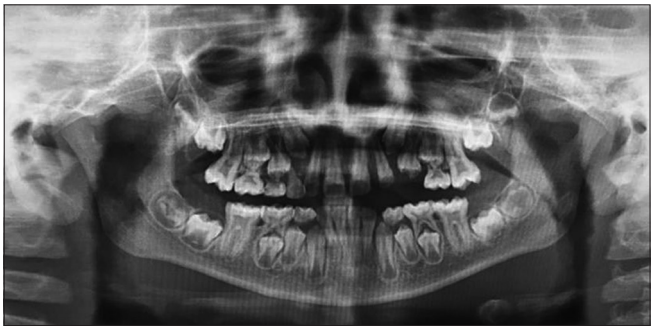

Figure 4: An orthopantomogram revealed mixed dentition with generalized severe enamel hypoplasia

amino-acid substitution of cysteine for arginine at codon 393 (p.Arg393Cys; ENST00000550325). Homozygous mutations in the VDR gene were suggestive of VDDR2A.

Case 2

Similar clinical features were noted in a 5-year-old male patient; intraoral examination showed mixed dentition with enamel hypoplasia, dentin defects and enlarged pulp chambers. Genetic DNA test was suggestive of VDDR2A [Figure 5].

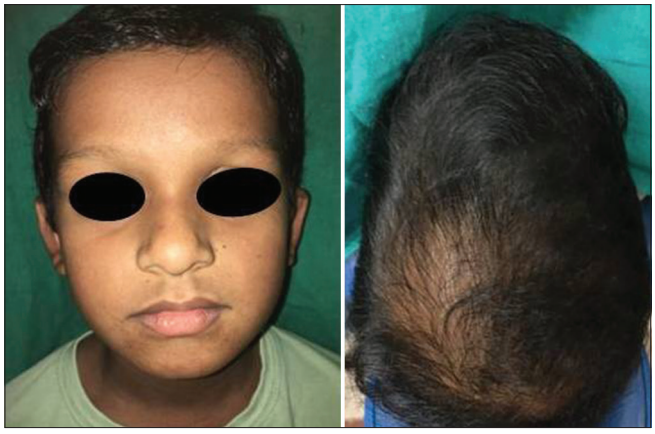

Figure 5: Profile picture with sparse hair

Both the cases were referred to a general physician for further management. They are currently under treatment for Vitamin D deficiency and alopecia. They were also explained about dental problems and their management.

DISCUSSION

VDDR2 is a rare form of hereditary autosomal recessive disorder, resulting from inactivating homozygous or compound heterozygous mutations in the VDR gene (OMIM*601769), encoding the Vitamin D receptor.[1,8] It is also known as pseudovitamin D-deficiency Type 2, hypocalcemic Vitamin D-resistant rickets or rickets-alopecia syndrome.[9]

The first case was reported in 1978 by Brooks *et al*.[10] in a 22-year-old woman with hypocalcemia, secondary hyperparathyroidism, osteomalacia and osteitis fibrosa cystica in association with normal serum 25-hydroxyvitamin D and markedly increased serum 1,25$[OH]_2$D with or without alopecia and named it as VDDR Type II.[10] Due to its rarity, delay in diagnosis and initial treatment, it results in deformities of lower limbs, severe growth retardation, acidotic breathing, cataracts, alopecia and presence of dental abscess.[11]

Table 1: Common causes of hereditary rickets

Gene/chromosome/MIM	Disease
Disorder of vitamin D metabolism	
CYP2Q1/11P15.2/608713	Vitamin D Hydroxylation – deficient Rickets Type 1B (also termed vitamin D dependant Rickets Type 1B) AR
CYP27B1/12q14.1/609506	25α-Hydroxy VitaminD-1α-hydoxylase deficiency (vitaminD dependant rickets Type 1A) AR
VDR: Vitamin D receptor/12q13.11/601769	Resistance to calcitriol and vitamin D–dependant rickets Type 2A, AR
Disorder of phosphate metabolism leading to rickets	
SLC34A1(sodium phosphate co-transporter family 34 member 1/5q35.3/182309)	Hypophosphatamic rickets with nephrolithiasis, Type 1, AD, fanconi syndrome Type 2, AR
SLC 34A3 Family 34, member3/9q 34/609826	Hypophosphatamic rickets with hyper calciuria, AR
SLC 9A3R1/Family member 3/17Q25.1/604990	Hypophosphatamic rickets with nephrolithiasis Type 2, AD
CLCN5: Chloride channel 5/XP11.23-p11.22/300008	X-linked recessive hypophosphatamic rickets, hypercalciuria, nephrocalcinosis, XLR
PHEX/XP22.1/300550	X-linked hypophosphatamic rickets, X–linked AD with increased expression of FGF23
DMP1/4Q22.1/600980	AR hypophosphatamic rickets with increase synthesis of FGF23
ENPP1/6q23.2/173335	AR hypophosphatamic rickets with increase expression of FGF23
FGF23/12P13.3/60538	(Gain of function) AD hypophosphatamic rickets associated with decrease degradation of FGF23

Table 2: Various laboratory findings in rickets with different etiology

Type	Calcium	Phosphate	Alkaline phosphatase	Calcidol	Calcitriol	PTH
Calcium deficiency	↑↓	↓	↑↑	N	↑	↑
Phosphate deficiency	N,↑	↓↓	↑↑	N	↑	N, ↓
Vitamin D deficiency						
Mild	N, ↓	N, ↓	↑	↓	N	N
Moderate	N, ↓	↓	↑↑	↓	N, ↓↑	↑
Severe	↓	↓	↑↑	↓↓	↓	↑↑
Loss of function CYP2R1 (25- hydroxylase)	↓	↓	↑	↓	↓	↑
Loss of function CYP27B1 (25OHD-1X-hydroxylase)	↑↑	↓↓	↑↑↑	N	↓↓↓	↑↑↑
Loss of function VDR (resistance to calcitriol)	↓↓	↓↓	↑↑↑	N	↑↑↑	↑↑↑
Loss of function PHEX (X-linked hypophosphatamic rickets)	N	↓↓	↑	N	N, ↓	N
Hypophosphatasia	N,↑	N,↑	↓	N	N	N, ↓

N-Normal, ↓ - Low, ↑- High

Rickets is classified based on common etiological factors into two types as calciopenic (defect in metabolism or functions of calcium/deficiency of Vitamin D) or phosphopenic (renal phosphate wasting).[2,3] Hereditary rickets is classified into two groups. The first group consists of genetic disorders of Vitamin D biosynthesis and action, such as VDDR1A, VDDR1B, VDDR2A and VDDR2B.[5] The second group involves genetic disorders of excessive renal phosphate loss (hereditary hypophosphatemic rickets).[6,7] Common causes of hereditary rickets [Table 1] and various laboratory findings in rickets with different etiology are enumerated [Table 2].[1] The present cases had alopecia with deformities, laboratory findings and genetic DNA test aides in the diagnosis of VDDR2A.

Clinical features include retarded growth, short stature and bone defects, leading to body deformities, bowing of legs, muscle weakness, convulsions and alopecia. To our knowledge, only a few authors have reported in literature describing the oral manifestations in VDDR2.[12] Oral findings include enamel hypoplasia, dentin defects and dental abnormalities and carious teeth. Dental radiologic features include dentin defects, short roots, large pulp chambers, poorly defined lamina dura, dental abscess and dental caries.[12,13]

The present cases reported here were seen with oral manifestations of enamel hypoplasia, dentin abnormalities, dental caries, impacted supernumerary teeth and large pulp chambers.

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 good response, but long-term administration results in complications such as cardiac arrhythmia, hypercalciuria, nephrocalcinosis, catheter related sepsis and extravasation of calcium.[1,14]

CONCLUSION

Calcium and phosphate metabolism plays a major role in bone mineralization, regulated by parathyroid hormone, $1,25[OH]_2D$ and FGF23. Vitamin D deficiency is an important cause of rickets and is most common. Vitamin D-dependent rickets is another form of bone disorder with rare oral manifestations, which is hereditary in origin, accounting for about 13% of total rickets. Early diagnosis and prompt treatment corrects the disturbed bone metabolism and dental deformities and improves the quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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