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Case Report

Vitamin D dependent rickets type 2: a case-based review of patient with alopecia and rickets

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ABSTRACT

Vitamin D dependent rickets (VDDR) type 2 is a very rare hereditary disease which has an autosomal recessive mode of inheritance. Patients with VDDR type 2 have a mutation in the gene encoding for vitamin D receptor on chromosome 12q12-q14, thus averting normal physiological action of 1,25 vitamin D. It's presents with the developmental delay in motor domain with features of rickets usually in the first year of life. Alopecia totalis has a frequent association with the disease. We are reporting a case of a 5-year-old boy who has a history of difficulty walking since 2 year of life, with a gradually progressive motor weakness course. Patients have a history of alopecia since 2 months of age, which progressed to alopecia totalis. On investigation, serum calcium was 7.2 mg/dl with a very high alkaline phosphate level of 1065 IU/ML with a normal vitamin D level was reported. The initial treatment started with IV calcium followed by 1000mg of oral calcium, along with a high dose of calcitriol. The patient was under periodic follow-up showing improvement in biochemical parameters. We reviewed literature of seven patient out of which 5 patients had alopecia and found 2 patients had enamel hypoplasia and all had features of rickets.

Keyword: VDDR, Alopecia, Rickets

INTRODUCTION

Hereditary vitamin D resistant rickets (VDDR) type 2 is an autosomal recessive disorder characterized by early onset of very severe rickets with alopecia.[1] It is caused due to mutation of gene on chromosome 12q12-14, which encodes for a vitamin D receptor.[2] Its biochemical parameters are hypocalcaemia, hypophosphatemia, hyperparathyroidism, and elevated circulating levels of 1,25(OH) 2 vitamin D3. The significantly elevated serum levels of 1,25(OH) 2 vitamin D3 distinguishes this disorder from 1-α -hydroxylase deficiency, which is associated with low levels of 1,25(OH) 2 vitamin D3.[3] As there is target organ resistance, the response to treatment is suboptimal.

CASE REPORT

A 5-year-old boy presented with complaints of loss of hair for 2 months of life with progressive motor weakness in the form of difficulty in walking at the age of 2 years, progressed to not able to walk independently. The child, who is the youngest among siblings, is the product of a non-consanguineous marriage with no such abnormality in siblings and parents.

Patient had history of difficulty in walking since age of two years which progressed to not able to walk by the age of 4 years, patient also had alopecia since 2 months of life. Patients had visited multiple doctors for the above complain and X ray was done. X rays shows typical features of rickets. As patient was diagnosed with rickets

patient was treated with vitamin D multiple times but patient had worsening course.

Then patient was referred to our centre. On history and clinical examination, typical features of VDDR type 2 was present. The patient had features suggestive of rickets, widening of the wrist, bowing of legs, frontal bossing as shown in figures. Patients too have loss of hair on the scalp, face and whole body as shown in Figure 3. Based on history and clinical findings, VDDR type 2 was suspected and further investigation was done. The X-ray is the anteroposterior of the bilateral wrist joint, showing osteopenia with metaphyseal fraying, splaying and cupping as shown in Figures 1 and 2. A biochemical tests were done showing low level of calcium with normal level of vitamin D. They were suggestive of VDDR 2, results are discussed in Table 1.

Table 1: Biochemical profile of the patient.

Variables	Reference range	Results
Serum calcium	8.5-10 mg/L	7.2
25-OH vitamin D	30-100 ng/dl	35.5
Alkaline phosphate	44-147 U/L	1065
Urea	10-40 mg/dl	15.71
creatinine	0.6-1.3 mg/dl	0.6
25(OH) D	20-100 ng/ml	42 ng/ml
1,25 (OH)2 D	20-80 pg /ml	310 pg/ml
ABG		Normal

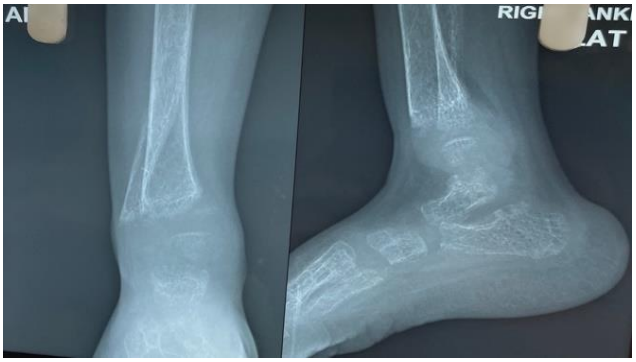

Figure 1: X ray of foot showing fraying, splaying.

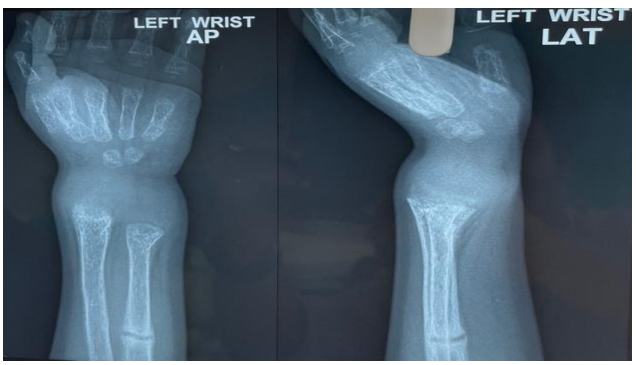

Figure 2: X ray of hand showing fraying splaying, cupping fracture and osteopenia.

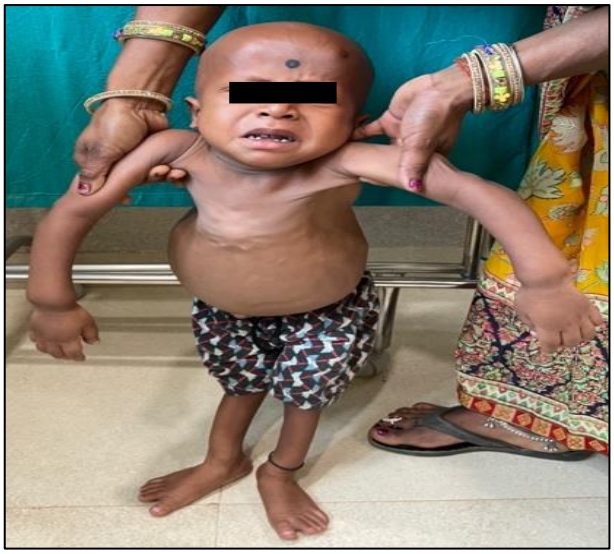

Figure 3: Alopecia, wrist widening, bowing of legs, Harrison sulcus and rachitic rosary.

After diagnosis, the patient advised about treatment. It included an intravenous dose of calcium gluconate followed by daily oral calcium at the dose of 1000 mg/day. The patient was also advised to use oral calcitriol at the dose of 2 micrograms daily. The patient was followed up for the next 4 months. There was improvement in biochemical parameters along with satisfactory healing of metaphysis on the x-ray. Even after 4 months of treatment, the patient remained alopecic. The patient was advised to continue treatment until significant recovery happens. After 6 months of therapy patient was lost to follow up.

Search strategy

We conducted a computerized search of PubMed and Scopus database using combination of term VDDR 2 alopecia and dental hypoplasia. Total of seven cases were selected and compared. Details of relevant cases are summarized in Table 3.

DISCUSSION

Vitamin D deficiency has become an emerging problem globally over the last few decades, not only in the western world but even in tropical areas or countries, despite having abundant sunlight. Worldwide, many countries such as Pakistan, Afghanistan and India reported extremely high prevalence, up to 20% of low vitamin D status.[4] Additionally, genetic causes of rickets (hereditary rickets) are rare, accounting for about 13% of total rickets.[5] The comprehensive nutrition survey, by ministry of health and family welfare (GOI), states that the prevalence of vitamin D deficiency as defined by adolescents' level of 25OHD <12 ng/ml, has been found to be 14% among children aged 1-4 years ,18% among school aged children (5-9 years) and 24% among adolescent.[6]

As there is a high prevalence of nutritional rickets, another aetiology of rickets is not frequently thought of. In the year 1937, Albright reported a case showing a child with features suggestive of rickets failing to respond to the recommended dose of vitamin D therapy, and suggested hereditary resistance to the action of calciferol as a basis of rickets.[7]

VDDR is a rare hereditary form of rickets with a mostly autosomal recessive mode of inheritance.[8] There are broadly three categories of VDDR. The first type is VDDR 1, represented as inability to generate 25 (OH) D(VDDR1b) or 1,25(OH) D (VDDR1a). In the second type, VDDR2, there is resistance to 1,25(OH) D because of mutation in a vitamin D receptor (VDDR2a) or there is abnormal expression of a hormone response element binding protein that interferes with the normal function of the vitamin d receptor although receptors are normal (VDDR2b). The third type is VDDR3, which ensues from excessive inactivation of vitamin D metabolites.[4,8] Table 2 outlines the various features of VDDR

VDDR2 is a very rare form of inherited rickets having an autosomal recessive mode of inheritance resulting from inactivation of a vitamin D receptor. In Brooks et al reported the first case of a 22-year-old woman with hypocalcaemia, secondary hyperparathyroidism with normal serum 25(OH)D and 1,25(OH)D with alopecia and called it VDDR type 2.[7,8] Pseudo vitamin D deficiency is another name for VDDR type 2. There are very few case reports from India but the exact prevalence of disease yet unknown.[9]

Table 2: Laboratory findings in VDDR of different etiology.

Types	Inheritance	Genes	Alkaline phosphate	Calcium	PTH	25(OH)D	1,25(OH)D
VDDR 1A	AR	CYP27B1	↑↑↑	↑↑	↑	N/↑	↓
VDDR 1B	AR	CYP2R1	↑	↓	↑	↓	↓
VDDR 2A	AR	VDR	↑↑↑	↓↓	↑	N/↑	N/↑
VDDR 2B	AR	UNKNOWN	↑↑↑	↓↓	↑	N/↑	N/↑
VDDR3	AD	CYP3A4	↑↑↑	↑↑	↑	↓	↓

N=normal, ↑= Increased, ↓=Decreased

Table 3: Summary of case report of VDDR.

References	Age/ sex (Years)	Clinical features	Biochemical finding			Treatment	Outcome
			Ca	25 (OH)	1,25 (OH)		
Prithi et al[3]	4/M	Rickets, alopecia and delayed dentition	↓	↓	↑	Calcium 1,25(OH)D	Improved
Thakur[5]							
Pt 1	14/M	Rickets, alopecia and enamel hypoplasia	↓	N	↑	*	*
Pt 2	5/M	Rickets, alopecia and enamel hypoplasia	*	*	*	*	*
Azemi et al[10]	2.1/F	Rickets and alopecia	↓	N	↑		
Mishra et al[11]	3/F	Rickets	↓	N	↑	Calcium vit D2 (High dose)	Improved
Sunuwar et al[12]	2.5/M	Rickets and alopecia	↓	N	↑	Calcium 1,25(OH)D	Improved
Sachin et al[13]	24/F	Rickets	↓	N	↑	Calcium vit D2 (High dose)	Improved
Our case	5/M	Rickets and alopecia	↓	N	↑	Calcium 1,25(OH)D	Improved

N=normal, ↑=Increased, ↓=Decreased, *=not mentioned

The clinical features of VDDR type 2 mostly encompass growth retardation, short stature and rachitic changes in the form of bowing of legs with widening of the metaphyseal end of limbs and fractures.[1,11] We have reviewed literature and found, Smita et al, Sunuwar et al, Sachin et al.[11-13] Our and other case reports mentioned in table 2 had similar findings. Alopecia is frequently associated with VDDR type 2. It was found that 50% of VDDR type 2a has alopecia.[1,12] Prithi et al, Thakur et al, Azemi et al and Aunuwar et al and our case has alopecia.[3,5,10,12] Few of the authors reported regarding enamel hypoplasia. Prithi et al and Thakur have reported about enamel hypoplasia as mentioned in Table 3.[3,5] The dental changes consist of root resorption, hypoplasia,

dentin abnormalities and enlarged pulp chamber in an orthopantomogram.[14] Various laboratory changes of hereditary rickets are mentioned in Table 2 and 3.

The management of VDDR type 2 consists of a high dose of calcitriol (1-6 microgm/day in two divided doses) along with 1000 mg of elemental calcium daily.[1,5] In the case of severe hypocalcemia, patients may require intravenous calcium gluconate to safeguard patients from the dreaded complications of hypocalcemia. Although the response to therapy is suboptimal, as in VDDR type 2 patient has end organ resistance to the active form of vitamin D.

CONCLUSION

The calcium and phosphate metabolism has a vital role in bone mineralization, regulated by PTH, 1,25(OH) D and FGF23. The biochemical and genetic analysis has given insight into the various form of VDDR. Early diagnosis of the disease and prompt treatment rectify the disturbed bone metabolism and improves the quality of life.

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