Diagnostic challenges of Vitamin D-Dependent Rickets Type 1a (VDDR1A) caused by *CYP27B1* mutation in resource limited countries: a case series from three families

Sommayya Aftab[1,2], Tahir Shaeen[1], Muhammad Nadeem Anjum[3], Ahmed Imran[4], Anjum Saeed[3], Abid Quraishi[4], Huma Arshad Cheema[3]

[1]Department of Paediatric Endocrinology and Diabetes, The Children's Hospital & The Institute of Child Health, Lahore.

[2] Consultant Paediatric Endocrinologist and Diabetologist, Hameed Latif Hospital, Lahore.

[3] Department of Paediatric Gastroenterology and hepatology, The Children's Hospital & The Institute of Child Health, Lahore.

[4] Department of Radiology, The Children's Hospital & The Institute of Child Health, Lahore.

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INTRODUCTION

- Vitamin D dependent rickets type 1A (VDDR1A) is an autosomal recessive condition due to inactivating mutation in *CYP27B1* which inhibits 1-alpha-hydroxylase enzyme leading to defective conversion of 25-OH vitamin D to 1,25-$(OH)_2$ vitamin D. (Figure-1)
- Clinical and bone profile of VDDR1A mimics vitamin D deficient and others vitamin D dependent rickets. However, normal or raised 25-OH vitamin D in presence of low 1,25-$(OH)_2$ vitamin D is diagnostic of VDDR1A.
- In developing countries like Pakistan diagnosing VDDR1A is a challenge due to lack of free availability of 1,25-$(OH)_2$D level and genetic testing.

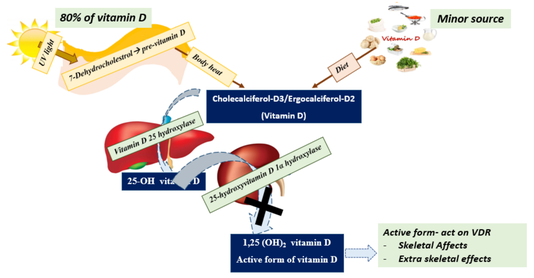


Figure-1 Pathophysiology Of Vitamin D dependent rickets type 1A

RESULTS

- Total 4 cases (all male) from three different families were identified.
- All were carrying homozygous *CYP27B1* mutation (c.1319_1325dup p.(Phe443Profs*24)).
- Age of start of symptoms is in late infancy (9-12 months).
- Mean age of presentation to tertiary care is 2.8 (1.5-3.9)years.
- All four cases presented with progressive bony deformities and failure to thrive. Three had repeated diarrhoeas and 1 had fracture.
- All born to consanguineous parents with case 1 having history of two sibling deaths due to rickets and repeated diarrhoeas. Case 3 & 4 are siblings.
- All four cases were treated as hypophosphatemic rickets before presentation.

Table-1. Clinical and bone profile at presentation

Anthropometry & Bone profile	Case 1	Case 2	Case 3	Case 4
Height (cm)	76	80	73.5	73
Weight (kg)	9	10	10	8.2
HV (cm/y)	2	0 .1	2	3
BMI (kg/m2)	15.58	15.62	18.51	15.39
Calcium (8.6-10.2)mg/dl	8.9	7.9	8.8	8.1
Phosphate (4 -7)mg/dl	2.2	2	1.5	1.6
Magnesium (1.5-2.5)mg/dl	2	2.2	2.5	2.1
Alkaline PO4 (IU/l)	3723	996	868	1148
25-OH vitamin D (ng/ml)	122	58.9	39.8	41.7
PTH (pg/ml)	771	80.9	110	213
Urine Ca : Cr	0.04	0.01	0.07	0.07
FeP (%)	17	23	23	24
TRP (%)	83	77	77	76

Failure to thrive with mean HV 1.7(0.1-3) cm/y and bone profile showing low-normal calcium, hypophosphatemia, phosphaturia, raised alkaline phosphatase and PTH)

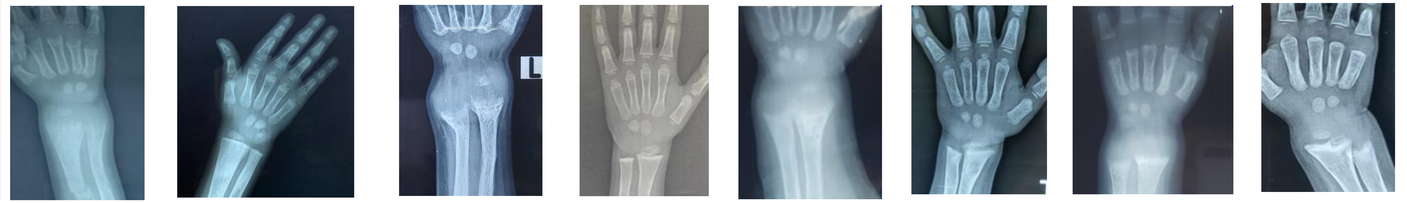
- Activated vitamin D (150 ng/kg/day)
  - Calcitriol (case 1&2)
  - Alfacalcidol (case 3&4)
- Calcium Supplementation

Table-2. Clinical and bone profile on 6-month follow-up

Anthropometry & Bone profile	Case 1	Case 2	Case 3	Case 4
Height (cm)	81	86	77	77
Weight (kg)	11	11.8	12	9.4
HV (cm/y)	12	10.9	7.7	8.7
BMI (kg/m2)	16.77	15.95	20.24	15.85
Calcium (8.6-10.2)mg/dl	9.3	10.6	9.3	9.2
Phosphate (4 -7)mg/dl	4.1	4.3	3.5	3.4
Alkaline PO4 (IU/l)	761	171	868	341
25-OH vitamin D (ng/ml)	49	47	58	54
PTH (pg/ml)	275	40	110	114
Urine Ca : Cr	0.04	0.2	0.08	0.07

Growing with mean HV 9.8(8.7-12) cm/y and having normal calcium, normal phosphate, reducing trend of alkaline phosphatase and PTH with normal urine calcium to creatinine ratio)

Radiological Outcome



AIM

- To determine the clinical profile and challenges in diagnosis and management of vitamin D dependent rickets type 1A in developing countries.

METHODS

- Retrospective review of all children with vitamin D dependent rickets type 1A due to *CYP27B1* mutation over last one year in a tertiary care hospital.

CONCLUSION

- We should have a high index of suspicion of VDDR1A in children with rickets not responding to cholecalciferol in resource limited countries.
- Calcitriol seems to be more efficient than alfacalcidol in term of healing of VDDR1A rickets.

REFERENCES

1. *Fukumoto S, Ozono K, Michigami T, Minagawa M, Okazaki R, Sugimoto T, Takeuchi Y, Matsumoto T. Pathogenesis and diagnostic criteria for rickets and osteomalacia - proposal by an expert panel supported by Ministry of Health, Labour and Welfare, Japan, The Japanese Society for Bone and Mineral Research and The Japan Endocrine Society. Endocr J. 2015;62(8):665-71*
2. *Kim CJ, Kaplan LE, Perwad F, et al. Vitamin D 1alpha-hydroxylase gene mutations in patients with 1alpha-hydroxylase deficiency. J Clin Endocrinol Metab 2007; 92:3177.*
3. *Edouard T, Alos N, Chabot G, et al. Short- and long-term outcome of patients with pseudovitamin D deficiency rickets treated with calcitriol. J Clin Endocrinol Metab 2011; 96:82.*