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Case Report

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Long term follow-up of vitamin D dependent rickets type IA caused by novel mutation in cyp27b1 in a 2.5 years old Pakistani boy: A case report

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Abstract

Rickets usually caused by deficiency of vitamin D and it's a condition which affects bone development and leads to softening and weakling of bones in children. But there are rare inherited problems reported which leads to rickets and these are, Vitamin D Dependent Rickets Type 1, Vitamin D Dependent Rickets Type 2 (also known as Vitamin D resistant rickets) and 25 hydroxylase deficiency rickets. Herein, reporting a case study of 2.5 years toddler boy with history of multiple hospital admissions due to seizures, initially managed as a case of florid rickets, but there was no improvement observed, so he was re-investigated and later diagnosed with Vitamin D Dependent Rickets Type 1A. It is a rare genetic disorder and inherited as autosomal recessive pattern due to inactivating mutations in CYP27B1 gene encoding the 1α-hydroxylase enzyme.

Keywords: Vitamin D dependent rickets; Autosomal recessive disease; Homozygous mutation.

Introduction

Vitamin D dependent rickets type I A is an Autosomal Recessive disorder caused by homozygous mutation in CYP27B1 gene. This disorder can present in infancy with delayed motor milestones (walking), signs of rickets, poor dentition, short stature, muscle weakness, or metabolic fits.

Vitamin D is one of the major hormones regulating blood levels of calcium and mineral homeostasis of the bone. It is an inactive prohormone that can be ingested or synthesized in the skin. The production of the active hormone, calcitriol or 1α,25dihydroxy vitaminD3 (1,25(OH)2D), results from sequential hydroxylation by members of the cytochrome P450 enzymes [1]. In short, 1,25(OH)2D facilitates bone mineralization by promoting osteoblast function and osteoclast differentiation while maintaining blood calcium and phosphate levels, through enhanced gastrointestinal and renal absorption. It also regulates its own activity by up regulating 24hydroxylase (which metabolizes 1,25(OH)2D) and Fibroblast Growth Factor23 (FGF23) and down regulating Parathyroid Hormone (PTH).

In this case study we describe the case on novel CYP27B1 mutation that presented with signs of florid rickets which after proper diagnosis and treatment responded well. In addition, treatment for this and follow-up regarding symptoms are further explained in the discussion section.

Case report

2.5 years old boy weighing 10 kg presented with history of seizures, recurrent chest infections and spontaneous fractures. He has his first fit at the age of 7 months, at that time he was diagnosed with Rickets and Stoss therapy was prescribed. Later at

the age of 22nd month he had his first spontaneous fracture for which orthopedic surgeon was consulted. During that time, he also visited a nephrologist and pediatrician and underwent multiple hematological and radiological investigations. Vitamin D and other supplement were prescribed but only little improvement was observed. At the age of 30 months he got admitted in our hospital with complain of fever and respiratory distress.

Our client is 4th product of consanguineous marriage. He has two siblings which are healthy and fine and an elder sister which died at the age of 2.5 years due to hypocalcemia and pneumonia.

Physical examination revealed signs of anemia, open anterior fontanelle, frontal bossing, poor dentition and delayed eruption of teeth, rachitic rosary and widening of wrist (Figures 1 & 2). His standard deviation score value for weight, height, and head circumference were -2, -6.4 and 0.13 respectively.

Blood calcium, phosphorus, and alkaline phosphatase levels were 6.2 mg/dL, 4.43 mg/dL, and 1561 IU/L, respectively. Serum levels of PTH (88.3 pg/mL, N:12-88) and 25(OH)D3 levels (45.67 µg/L) and 1,25(OH)2D3 level (6.8 pg/mL, N:15-90 pg/mL) was low his biochemical profile at the time of diagnosis and follow up after treatment (Figure 4). His arterial blood gases and Tubular resorption of phosphorus was normal.

Skeletal survey showed remarkable signs of reduced bone density, florid periosteal reaction, widening of long growth plate with splaying, cupping and fraying. Bowing of both fibula medially, slayed and frayed head of metacarpals and metatarsals bilaterally, favoring rickets (Figure 3).

The molecular genetic study revealed homozygous CYP27B1 gene (Figure 5).

Patient is treated with conventional therapy of calcitriol with dose ranging from 0.4 mcg/ day and calcium of 600 mg/ day with follow up showed normalization of phosphorus but hypocalcemia persisted so dose was increased to 0.7 ug/day.

Currently he is taking 1 mcg/day and calcium of 700 mg/day which result in improvement of his clinical findings biochemical parameter and x-ray. His elder sister died at of 2 years with similar complains where as no diagnosis made. Mother had significant history of abortion.

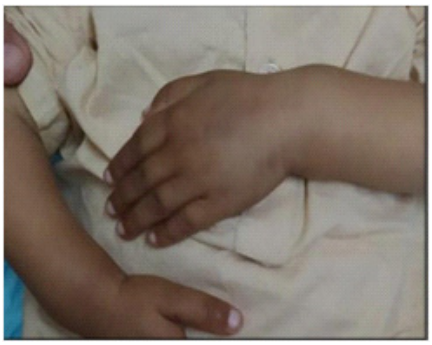
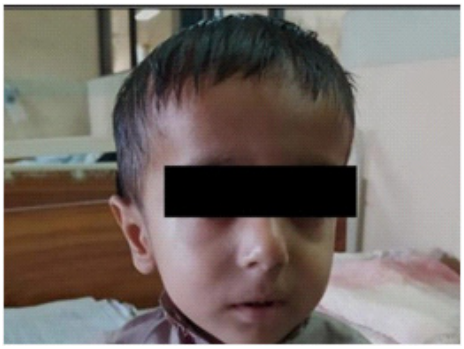


Figure 1:



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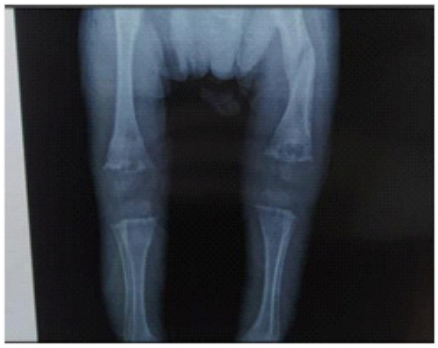

Figure 3:

	2019-Jun	2019-Aug	2019-Oct	2019Dec	2020-Feb	2020-Aug	2020 dec	2021 feb	2021-AUG	Normal
Ca	6.2	6.4	8.2	5	5.7	4.5	5.4	7.0	7.3	8.5-1.5
Mg	2.3			1.62	1.78				2.4	
Po4	2.43	4.0				6.07	7.35	5.87	5.0	2.5-5.5mg/dl
AlkPo4	1561	1400		1178			1415	750	600	<645
PTH	100	88.3			619					12-88
Vit D2			45.67					>70		44

Urinary Ca/Cr ratio was normal and no evidence of nephrocalcinosis in followup.

Figure 4:

RESULT: POSITIVE

Two Pathogenic variants identified in CYP27B1. CYP27B1 is associated with autosomal recessive vitamin D-dependent rickets.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CYP27B1	c.171dup (p.Leu58Alafs*275)	homozygous	PATHOGENIC
SLC34A1	c.1699G>A (p.Gly567Arg)	heterozygous	Uncertain Significance

Figure 5:

Discussion

To regulate levels of calcium in blood and to achieve homeostasis of minerals within bone, vitamin D plays a very pivotal role, by promoting osteoblast function and osteoclast differentiation and mainly maintaining Calcium and Phosphorus blood levels via increased GIT and renal absorption. Vitamin D also regulates it's own activity by up-regulating 24- hydroxylase and fibroblast Growth Factor 23 and down regulating PTH [1].

So any deficiency in vitamin D or metabolic pathway of Vitamin D leads to rickets, which is imperfect mineralization of growth plate of epiphysis it is characterized by growth retardation and skeletal deformities in children [2]. It presents with symptoms of hypocalcemia such as poor feeding, muscle weakness, seizures failure to thrivehypocalcemiafits [2,3].

Vitamin D is either synthesized in the skin or consumed from the diet [1]. There are two forms of Vitamin D Ergocalciferol (D2) and Cholecalciferol (D3), they are biologically inactive prohormones [1,4]. To work properly, Vitamin D must undergo two enzymatic hydroxylation conversion in liver and kidney by 25 and 1 hydroxylases respectively [4,5].

Vitamin D3 can also formed under skin from 7-dehydrocholesterol due to exposure to UV -B radiation. Where as D2 is acquired from plants. They both follow same metabolic pathway to convert into same active 1,25 dihydroxy or Vit D form by sequential hydroxylation by cytochrome p450 enzymes. In liver first hydroxylation step is 25 alpha hydroxylation is performed by CYP2R1 to convert into 25 hydroxy vitamin D. Next activation step is highly regulated in kidneys by PTH, hypocalcemia and hypophosphatemia. Where 25OHD converts into 1,25 dihydroxy Vitamin D, which binds to vitamin D receptors in nucleus to increase the expression of gene which modulate Calcium and Phosphorus hemostasis [1,4,5].

Initial studies showed that nutritional deficiency along with sunless environment leads to rickets and it could be treated with cod liver oil. Later it was observed by many other investigators and researchers that sunlight can also prevent rickets [1,6].

Although prevalence and clinical burden declined due to commercial development of vitamin D (Calciferol), but it was observed that some patients have failed to respond usual regime of calciferol and this observation leads to clinical and genetic disorders that hinders in activation of pro vitamin D hormone or end organ resistant to Vitamin D [6].

Vitamin D Dependent rickets type 1A or 1 alpha hydroxylase deficiency also known as pseudo Vitamin D deficiency is a rare autosomal recessive disorder with imparied activation of Vitamin D caused by CYP27B1 mutation which encode 1 alpha hydroxylase enzyme [4,5].

1 alpha OH gene cloned and mapped on chromosome 12q13.1-913.3 and its composed of 9 exons and to-date more than 70 has been reported.

VDDR 1 is a pathophysiology misnomer, but as lifelong dependency of patient on specialized regimens of Vitamin D replacements, so there is relevance of its continued use [1,6].

VDDR 1 appears normal at birth but clinical picture become evident at 2-24 months & has same clinical and radiological findings as of rickets. Its laboratory features include hypocalcemia, hypophosphatemia, increase S.PTH, and low or undetectable serum levels if 1,25(OH)D despite normal or increase concentration of 25 OH D [1]. They may present with secondary reduced urinary calcium excretion, aminoaciduria and hyperchloremicacidosis [5].

Usually alpha calcidol and calciferol along with calcium supplements leads to good response in patient of VDRR 1 [1,4,6]. The goal of therapy in VDDR 1 is to serum Calcium levels within mid normal range to achieve normal serum levels of parathyroid hormone, which leads to correction of hypophosphatemia by restoring normal renal TRP. Patient should be followed every 3-6 months with S.Ca, Po4, PTH, AlkPo4, Cr and vit D metabolites to recognize hypo or hypercalcemia and to ensure normal growth and resolution of rickets. Treatment must be continued for indefinitely [6].

Learning points

Although a rare disorder, VDDR type 1 must be considered even in countries where vitamin D deficiency is common.

Genetic analyses are beneficial for early diagnosis and further management of probable familial cases.

VDDR type 1 require lifelong Vitamin D supplements, monitoring and regular follow up.

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