Novel homozygous mutation in CYP27B1 gene of vitamin D dependent rickets type 1A: a case report

Mohammed Al Dubayee[1, 2*], Reem Al Fattouh[1], Fahad Al Juraibah[1], Fuad Al Mutairi[1, 2], Amir Babiker[1, 2]

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ABSTRACT

Background: Vitamin D is a vital hormone in preserving calcium and phosphorus homeostasis in the body and maintaining normal growth and mineralization of bones.

Case Presentation: We identified a patient with vitamin D dependent rickets type 1A (VDDR1A). This patient had rachitic skeletal manifestations, macrocephaly, retarded motor development, hypocalcemia, hypophosphatemia, markedly elevated alkaline phosphatase, and secondary hyperparathyroidism associated with normal 25 hydroxyvitamin D [25(OH)D] and low 1,25-dihydroxyvitamin D [1,25(OH)2D]. These biochemical abnormalities are consistent with the diagnosis of VDDR1A. Molecular analysis of CYP27B1 gene revealed novel homozygous mutation "Gly125Arg". Unaffected parents were heterozygous carriers.

Conclusion: It is highly suggestive that "Gly125Arg" is the molecular defect causing this disease in our patient. Gly125Arg is likely to be a pathogenic mutation that leads to VDDR1A.

Keywords: CYP27B1 gene, dependent rickets, 1,25-dihydroxyvitamin D, 25 hydroxyvitamin D, VDDR1A, vitamin D.

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Corresponding Author: Mohammed Al Dubayee
*Department of Pediatrics, King Abdullah Specialized Children's Hospital, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.
Email: m.aldubayee@gmail.com
Full list of author information is available at the end of the article.

Background

Vitamin D is a vital hormone in preserving calcium and phosphorus homeostasis in the body and maintaining normal growth and mineralization of bones [1]. In the absence of vitamin D, only 10–15% of dietary calcium and 60% of phosphorus will be absorbed. In addition, vitamin D plays a role as immunomodulator, in fighting infection and reducing cancer risk.

Vitamin D is mainly produced by the effect of ultraviolet light on 7-dehydrocholesterol in human skin and, to a lesser extent, from ergocalciferol that is produced by plants. Both forms are initially hydroxylated in the liver to form 25-hydroxyvitamin D, which is the most abundant form in the body but with minimal effect on vitamin D receptors. 25-hydroxyvitamin D is further hydroxylated in the proximal renal tubules, by the effect of 1α-hydroxylase, to form the active and potent 1,25-dihydroxyvitamin D [1,25(OH)2D]; a step tightly regulated by parathyroid hormone (PTH) and calcium and phosphorus levels.

Vitamin D deficiency is the most common cause of rickets. Nevertheless, two other rare autosomal recessive genetic disorders are found to cause rickets. A defect in the gene encoding 25-hydroxyvitamin D3-1-alpha-hydroxylase (CYP27B1 gene) on chromosome 12q13, results in the inability to form the active 1,25(OH)2D. This disease is known as vitamin D-dependent rickets type 1A (VDDR1A) (OMIM#264700). On the other hand, a defect in the (VDR <AQ: Please provide expansion for "VDR."> gene) on chromosome 12q encoding the vitamin D receptor will lead to end-organ unresponsiveness to vitamin D causing an increase in the circulating ligand, 1,25(OH)2D3. In such a case, most patients will have total alopecia in addition to rickets. This disease is known as vitamin D-resistant rickets type 2A (OMIM# 277440) [2].

Children affected with VDDR-1 usually present in their infancy with a clinical presentation of severe rickets including growth retardation, hypotonia, and hypocalcemic seizures with typical radiologic findings of rickets. Biochemical investigations usually reveal hypocalcemia, secondary hyperparathyroidism, increased alkaline phosphatase levels, and low or undetectable 1,25(OH)2D levels despite normal or high levels of 25-hydroxyvitamin D.

In this report, we describe a case with VDDR1A who had a novel genetic mutation followed by discussion and literature review.

Case Presentation

A 17-month-old Saudi girl had been suffering from motor developmental delay, delayed dentition, and macrocephaly since the age of 9 months. She was only capable of sitting without support. Other developmental domains were appropriate for her age. She had no teeth eruption in addition to her enlarged head with no other significant symptoms. She was on a balanced diet. Her perinatal history was unremarkable. Her parents are consanguineous and

our patient was their first child. They have no history of metabolic bone disease running in the family. The patient was seen previously in another healthcare facility, before being assessed in our tertiary center, and was started on vitamin D supplements with no improvement. On examination, both height and weight were below the 5th centile. Her head circumference was above the 95th centile with a large anterior fontanel. She had no teeth eruption in addition to Harrison's sulcus, rachitic rosary, and widening of her wrists. She had normal hair distribution with no signs of alopecia. Other systemic examination was unremarkable.

Initial labs showed low levels of calcium and phosphorus, markedly elevated levels of PTH and alkaline phosphatase, normal total 25-hydroxyvitamin D level, and undetectable levels of 1,25(OH)2D, the active form of vitamin D. Wrist X-ray demonstrated advanced features of rickets in the form of fraying and cupping of the metaphysis, diffuse osteopenia, and widening of the growth plates (Figure 1).

Patient's findings were highly suggestive of VDDR1A. As a result, she was started on high dose 1α-hydroxycholecalciferol and calcium supplements. Molecular testing for CYP27B1 revealed a novel homozygous mutation in the gene (c.373G>Ap.Gly125Arg). This amino acid substitution was not observed in any database and it occurs at a position that is conserved across species. In silico analysis predicts that this variant is probably damaging the protein structure/function. Parents were tested for this mutation and they were found to be heterozygous carriers.

The patient had close follow up on treatment and she improved significantly. Her weight and height are currently on the 5th and 10th centiles, respectively. Her head circumference is still above the 95th centile. She can now walk with support. Her PTH, alkaline phosphatase, and 1,2-dihydroxyvitamin D are normalizing (Table 1). Repeated wrist X-ray, six months after starting therapy, showed substantial improvement (Figure 2).



Figure 1. *Wrist X-ray of the patient at presentation.*

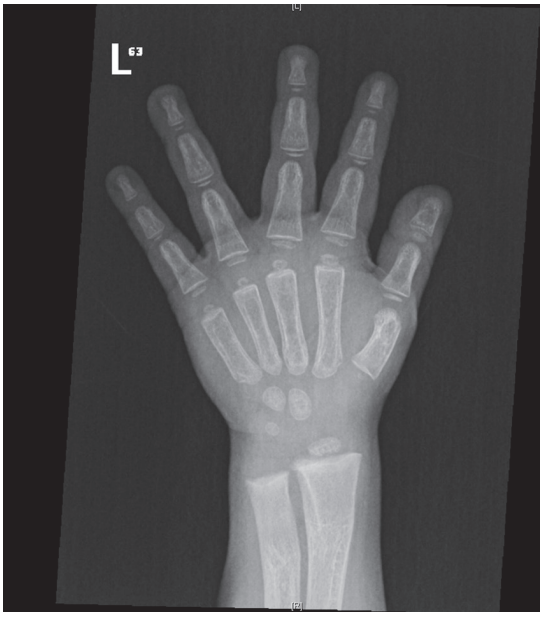


Figure 2. *Wrist X-ray of the same patient after 6 months of therapy.*

Table 1. Biochemical bone profiles of the patient at presentation and during treatment.

TEST	REFERENCE VALUE	AT PRESENTATION	2 MONTHS OF THERAPY	6 MONTHS OF THERAPY
Alk Phos	≤500 U/L	>4555	2047	866
Adj Ca	2.25-2.75 mmol/L	2.1	2.24	2.33
Phos	1.10–1.95 mmol/L	0.77	0.85	1.52
PTH	1.60–7.20 pmol/L	73.88	16.27	4.65
Total 25-OH Vit D	75–120 nmol/L	96.1	78.5	79.8
Vit D 1,25	62.6–228.0 pmol/L	<15.6	NA	49.7

Alk Phos: alkaline Phosphatase, Adj Ca: adjusted Calcium, Phos: Phosphorus, PTH: parathyroid hormone, Total 25-OH Vit D: 25-hydroxyvitamin D, Vit D 1,25: 1,25 dihydroxyvitamin D.

Discussion

Our patient's clinical and biochemical abnormalities are consistent with the diagnosis of VDDRIA. Molecular analysis of CYP27B1 gene revealed novel homozygous mutation "Gly125Arg." Unaffected parents were heterozygous carriers. This data is highly suggestive that "Gly125Arg" is the molecular defect causing this disease in our patient.

The human CYP27B1 gene encodes 1α hydroxylase, which is considered one of the important enzymes and represents a regulatory step in vitamin D biosynthesis. This enzyme is responsible for hydroxylation of 25(OH) D to the active form 1,25 (OH)2 D [3]. In 1990, CYP27B1 was initially mapped to chromosome 12q13-14 by linkage study then was subsequently cloned first in mice then in humans in 1997 [4]. It is composed of nine exons and eight introns [5]. The Gly125Arg mutation, which results in substitution of glycine by arginine, has not previously been identified. This amino acid substitution occurs at a position that is conserved across species and in silico analysis; this variant is predicted to damage the protein structure or function. Different mutations affecting the same amino acid residue has been reported "G125E" [6], this type of mutation abolishes the activity of 1 alfa hydroxylase by reducing its affinity to 25 hydroxyvitamin D [25(OH)D]. It has been suggested that mutation in Gly125 was associated with damaging the tertiary structure of the substrate-heme pocket of CYP27A1, which belongs to the same family as CYP27B1 [7]. The other reported mutations located in exon 2 G102E, R107H, and P112L were found to be in the substrate recognition site and/or affecting heme-binding residue [6]. Regarding un-conserved residues, Thr409 was shown to be a critical amino acid residue as it forms a hydrogen bond with 25-hydroxyl group of 25(OH)D3 [8].

There is no strong genotype–phenotype correlation. Mild VDDR1A cases with different mutations have been reported (E189G, E189K, and L343F) although the enzymatic activity was completely absent [9]. Additionally, G102E mutation was identified in a large family where the disease expression was widely different [10]. These diversities in clinical presentation indicate that other factors could be involved and affect the severity of the disease. Providing that our patient was not suffering from recurrent bone fractures or seizure as reported in other cases, her disease is considered to be mild to moderate in severity [9].

Previously reported VDDR1A cases have been diagnosed around the same age [1,9,10]. Our patient presented earlier to another hospital when the diagnosis was unfortunately missed. VDDR1A can be inappropriately confused with other pathology like hypophosphatemic rickets, as both of them are associated with low serum phosphate level, hypocalcemia, and markedly elevated alkaline phosphatase. However, high PTH level indicates the likelihood of VDDR1A and helps to differentiate between these two pathologies.

VDDR1A cases respond well to alfacalcidol or calcitriol. Physiologic amount of calcitriol (10–100 ng/kg/day) completely resolves clinical, biochemical, and radiological manifestations. However, stopping of treatment for a short period was associated with rebound of biochemical abnormalities [10]. Lifelong therapy is required aiming to correct hypocalcemia without hypercalciuria, improvement of muscular function, and healing of skeletal manifestations.

Conclusion

We report on a case with a novel CYP27B1 mutation that has mild to moderate phenotype that completely resolved with the appropriate treatment. In addition to CYP27B1 mutations, other factors seem to modify the disease severity and may need to be explored in a larger observational study for group of patients of VDDR1A.

Acknowledgement

None

List of Abbreviations

PTH	Parathyroid hormone
VDDR1A	Vitamin D-dependent rickets type 1A
VDDR2A	Vitamin D-resistant rickets type 2A

Consent for publication

An informed consent was obtained from patient and parents.

Ethical approval

Ethical approval is not required at our institution to publish a case report in a medical journal.

Authors' details

Mohammed Al Dubayee[1, 2], Reem Al Fattouh[1], Fahad Al Juraibah[1], Fuad Al Mutairi[1, 2], Amir Babiker[1, 2]

1. Department of Pediatrics, King Abdullah Specialized Children's Hospital, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

2. College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

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Summary of the case

Patient (gender, age)	1	17 month old, Female
Final Diagnosis	2	Vitamin D-dependant rickets type 1A (VDDR-1A)
Symptoms	3	Poor height and weight gaining and delayed motor development. Large head and anterior fontanel. No teeth eruption or alopecia
Medications	4	Active form of vitamin D (1-alpha) drops
Clinical Procedure	5	Biochemical, genetic and radiological work up
Speciality	6	Pediatric Endocrinology