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Vitamin D Dependent Rickets Type 1a as a Rare Cause of Rickets: Case Report and Literature Review

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Abstract **Case Report**

***Aim*:** The purpose of this paper is to describe one example of type Ia, vitamin D-dependent rickets. Methods: A diagnosis has been made based on physical examination, laboratory results, and radiographic examination. A positive gentic mutation has also been used to corroborate the diagnosis. Results: Here, we present a case of a 2-year-old Saudi girl who exhibits delayed motor development and valgus deformity of the feet together with biochemical and radiographic signs of vitamin D abnormalities. She was initially treated at a peripheral hospital for rickets as Vitamin D deficiency and given cholecalciferol for six months; however, there was little improvement. Later, she was referred to us, and we performed a genetic study that revealed a positive gentic mutation at CYP27B1, confirming the diagnosis of Vitamin D dependent Rickets 1a, and Calcitriol treatment followed. Within 4 weeks, the patient exhibits significant recovery, and both PTH and alkaline phosphatase levels return to normal. After three months of calcitriol treatment, clinical and radiological proof of the improvement was observed. Conclusions: In this research, we raise the knowledge that rickets is not always caused by vitamin deficiency and that early presentations should increase awareness of inherited causes of rickets such VDDR1a that do not react to cholecalciferol and gentic investigation is helpful in such cases.

Keywords: Rickets, CYP27B1, VDDR1a, 25-hydroxylase enzyme.

INTRODUCTION

Rickets is still mostly brought on by a traditional vitamin D shortage in youngsters all over the world. This insufficiency is largely explained by a combination of unfavorable social, climatic, and nutritional circumstances. Rickets continues to affect people of all ages, even in warm nations like Saudi Arabia [1, 3].

In the Kingdom of Saudi Arabia, the prevalence of vitamin D deficiency (level less than 25 nmol/L) and vitamin D insufficiency (level 25-50 nmol/L) is 44.5% and 49.9%, respectively, with a total prevalence of 95.4% angham *et al*., [2]. One must comprehend the activation mechanism of rickets in order to correctly identify the disease's root cause.

Figure 1 depicts the activation route for vitamin D. 5-dihydrotachysterol is converted in the skin to cholecalciferol (vitamin D-3). This steroid passes through two phases of hydroxylation. The first phase of hydroxylation occurs in the liver by the enzyme 25-hydroxylase, which results in 25(OH) D3, and the second step occurs in the kidney's proximal convoluted tubules by the enzyme 1-hydroxylase, which results in hormonally active 1, 25-dihydroxyvitamin D3.

Rickets may result from any flaw in this system or from low levels of bone Ca, Po4, or ALP. At KSA, vitamin D dependent rickets type 1A has been thoroughly documented [18].

The 1-hydroxylase gene (CYB27B1) is mutated in this autosomal recessive disorder. Because nutritional rickets and hypophosphatemic rickets might be confused with it, genetic study is essential for making a correct diagnosis.

Hypotonia, muscle weakness, inability to walk, growth failure, and rickets-like radiological abnormalities are all unspecific features of VDDR1A [18].

VDDR 1B, (MIM 600081), is an autosomal recessive disorder, caused by Mutations of CYP2R1 gene responsible to produce 25 Hydroxylase enzyme in the liver [3-7].

It is a very rare condition that has been reported to currently affect around Seven families [7-12] patients will have low level of vitamin D 25, this is why it is common to miss it and wrongly labeled and treated as being vitamin D deficiency. In KSA, VDDR1B have been reported in 3 papers [2, 12, 13]. Those patients with VDDR1B) will respond to calcidiol Vitamine D which is already hydroxylated with 25 hydroxylase enzyme) [7, 8].

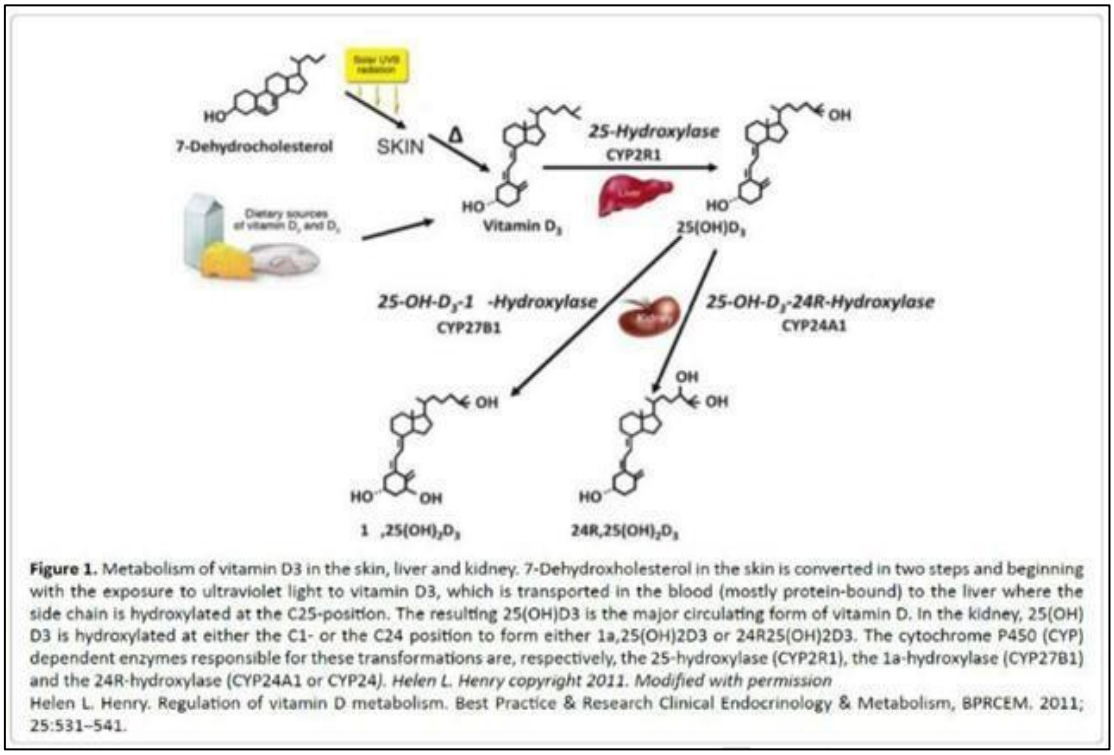


Figure 1. Metabolism of vitamin D3 in the skin, liver and kidney. 7-Dehydroxholesterol in the skin is converted in two steps and beginning with the exposure to ultraviolet light to vitamin D3, which is transported in the blood (mostly protein-bound) to the liver where the side chain is hydroxylated at the C25-position. The resulting 25(OH)D3 is the major circulating form of vitamin D. In the kidney, 25(OH) D3 is hydroxylated at either the C1- or the C24 position to form either 1a,25(OH)2D3 or 24R25(OH)2D3. The cytochrome P450 (CYP) dependent enzymes responsible for these transformations are, respectively, the 25-hydroxylase (CYP2R1), the 1a-hydroxylase (CYP27B1) and the 24R-hydroxylase (CYP24A1 or CYP24). *Helen L. Henry copyright 2011. Modified with permission*
Helen L. Henry. Regulation of vitamin D metabolism. Best Practice & Research Clinical Endocrinology & Metabolism, BPRCEM. 2011; 25:531–541.

History

In this report, we discuss a 2-year-old Saudi girl with delayed walking and deformed feet who previously had no history of convulsions, malabsorption, or any other chronic illness. She had a sufficient nutritional history and wasn't solely breastfeeding.

She had positive consanguinity, no history of rickets in her family, and her mother's vitamin D25 levels were normal during pregnancy.

Cholecalciferol, Calcium globionate was used to treat the patient at another hospital for six months, but there was no discernible change.

Upon inspection, she has rachitic rosary and frontal bossing. Her weight was -1 SD but growth parameters indicate that she has growth restriction, genu valgus in her lower limbs, and slight hypotonia.

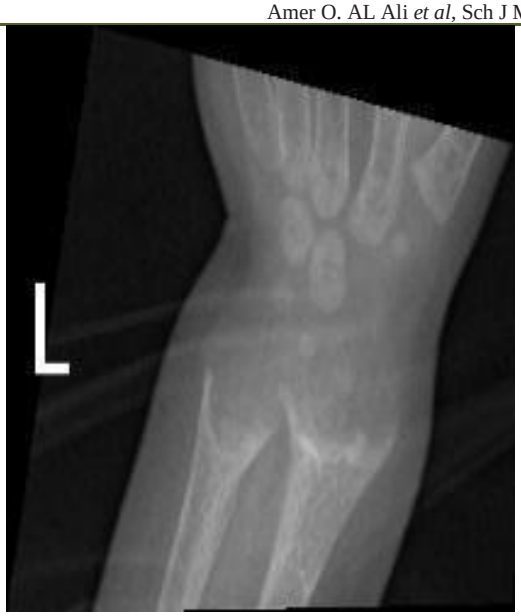
Other systemic examination was unremarkable.

Test	Result	Normal Range
vitamin D25 level	50 ng/dl (normal)	30-70 ng /dl
Vitamin D1, 25	6 pg/ml (low)	15-75 pg/mL),
PTH	130 pmol /l (high)	2-7 Pmol/l
ALP	2400 U/L (high)	150- 350 u/ l
Phosphorus	0. 45mmol/L (low)	1. 2 -2. 8 MMOL /
Calcium	1. 7 mmol/L (low)	2. 2-2. 8 mmol/L
Ca /Creatinine ratio in urine	0. 1 mmol (low)	Less than 0. 2

Other electrolyte and CBC, Renal, Liver function, Celiac screening was normal investigations.

Radiology

X. ray show active rickets, which was resolved 3 months after calcitriol



Gentic study:

WES identified the homozygous variant c .1286G>C p (Arg429 pro) in exonB of the CYP27B1 GENE (OMIM 60956) confirming diagnosis of VDDR1A.

Diagnosis and Treatment

Since the patient had been taking cholecalciferol for six months without experiencing any improvement, we concluded that the patient had VDDR type 1a or 1b. Since both were expected to respond favorably to calcitriol, a dose of one microgram daily was started. Later, the results of a genetic study revealed a gentic mutation at CYP27B1, which confirmed the diagnosis of VDDR1A.To prevent hunger bone syndrome, 50 mg/kg/day of elemental calcium was supplied for a month.

Surprisingly, all biochemical indicators, including ALP, PTH, CA, and Po4, were restored after 4 weeks of calcitriol, and after 5 months of calcitriol, the child began to move at the age of 3 months.

DISCUSSION

Rickets is a widespread bone mineralization illness that affects people all over the world. The majority of cases are brought on by a vitamin D 25 shortage that can be identified based on a history of inadequate nutrition, being more prevalent in infants who are exclusively breastfed and those who get little sun exposure. Infants born to mothers who did not receive treatment for vitamin D deficiency during pregnancy.

Most doctors will use cholecalciferol to treat children with rickets and low levels of vitamin D 25. And the majority of them will benefit from this therapy. However, a patient could occasionally not react favorably to cholecalciferol. In such circumstances, one should reflect and consider the patient's lack of response. Poor compliance is one reason for a poor reaction, an insufficient dosage, and malabsorption are checked out, one should consider the uncommon inherited genetic causes of rickets, such as VDDR 1a or 1b or resistant type VDDR TYPE 2, instead.

Our patients who had Rickets that manifested clinically, radiologically, or biochemically at an early age (6 months) and who had been treated at another institution for a vitamin D deficiency and given cholecalciferol for 6 months but had shown little improvement were sent to us.

After reviewing her past, we discovered that she was not exclusively breastfeeding, that her dietary history was appropriate, that the mother's vitamin D level was normal, but that the baby's vitamin D1.25 level was incredibly low while the mother's vitamin D25 level was normal.

Since the child was not responding to cholecalciferol, we considered the potential that the patient may have inherited rickets from a genetic origin, such as VDDR 1A or 1B, both of which will respond to calcitriol, which was empirically started before we received the results of the genetic result.

The patient was then put on 1 mic oral calcitriol, and after a few weeks, the patient's levels of ALP, PTH, Ca, and Po4 returned to normal.

Three months following calcitriol, radiological evidence of healing was clear and patient continue to do fine on Calcitriol 1 mic, and started to walk at age of 2.7 years.

The preferred medication for the treatment of VDDR1a is ALFACALCIDOL (one alpha), a type of vitamin D that has already undergone hydroxylation by the 1 alpha enzyme and requires the liver's 25

hydroxylase enzyme to work normally in order to be active.

Due to the same clinical, biochemical, and radiological features of active Rickets, including low levels of Vitamin D 25, VDDR1b is sometimes misdiagnosed with a simple Vitamin D insufficiency. The CYP2R1 gene for VDDR1B [2, 4, 15, 16], together with early presentation, a favorable family history, and a poor response to Cholecalciferol and One alpha therapy in VDDR 1b, are the best ways to distinguish between them.

The preferred medication for VDDR1B is CALCIFEDIOL (CALCIDIOL, 25 HYDROXY-CHOLECALCALCIFEROL), which is vitamin D hydroxylated with 25 enzyme and doesn't require the addition of cholecalciferol because it only requires normal kidney function of 1 alpha enzyme.

Calcitriol is the best option because it works for both types of VDDR 1A and 1b when the diagnosis is unclear. Even type VDDR 2 resistance may responds to Calcitriol but requires a greater dosage with intermittent iv calcium [5, 6].

Vitamin D-dependent rickets type 1B (VDDR1B) has been linked to CYP2R1 mutations. The molecular study of 7 patients from unrelated families who presented with VDDR type 1B due to a novel mutation and a loss-of-function CYP2R1 mutation was described by Molin A *et al.*, in 2017 [7]. They recognized the distinct biochemical pattern of the illness and how 25-hydroxyvitamin D therapy significantly improved it.

With a strong family history of vitamin D insufficiency, Almutair *et al.*,'s [12] observations of vitamin D deficient symptoms and a poor response of 25(OH)D3 levels to D2 or D3 treatment should raise the possibility of genetic reasons for CYP2R1 mutations (VDDR1B).

When receiving vitamin D, patients with CYP2R1 mutations have normal or high levels of 1, 25(OH)2D3, and they require supraphysiological dosages of cholecalciferol to have full or partial recovery [8–12].

Interestingly, adult patients with VDDR1B were able to maintain normal mineral metabolism without vitamin D treatment [7]. The prognosis is favourable.

According to their homozygous/heterozygous status and the underlying genetic mutation, patients with VDDR1B (CYP2R1) treatment with supra-therapeutic doses of oral vitamin D in addition to oral calcium showed minimal to moderate clinical and biochemical response, with homozygous patients responding noticeably less than heterozygous patients. Despite having a stronger reaction, heterozygous patients were unable to reach the ideal level of 25-OH vitamin D [3].

CONCLUSION

Gentic research is crucial for identifying the different kinds of rickets. Since each cause required unique therapeutic strategy.

The possibility of hereditary causes of rickets, such as VDDR1a or VDDR 2, should be raised in patients with RICKETS who have NORMAL vitamin D25 levels.

Since it works for both type VDDR1 OR type VDDR2 (HIGER DOSE), CALCITRIOL is the best option when the diagnosis is unclear or the patient is currently taking vitamin D supplements.

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