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Case Study

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A NOVEL CYP27B1 GENE MUTATION: A RARE CAUSE OF TREATABLE VITAMIN D DEPENDENT RICKETS TYPE1A: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Background: Vitamin D deficiency is the most common cause of rickets followed by liver and renal diseases that affect vitamin D metabolism. Rare genetic errors of vitamin D metabolism can cause rickets. One of the three rare genetic errors of vitamin D metabolism is CYP27B1 gene which encodes 1α-hydroxylase. It is the genetic base for vitamin D dependent rickets type1(VDDR-1). **Case Presentation:** A 22year Saudi woman presented with the history of slow development in growth, joint pains and difficulty in walking since early childhood. She diagnosed to have rickets with typical physical and radiological features. She was treated with calcium and vitamin D supplements in different hospitals. As her symptoms persisted she was referred to our endocrine department. On further investigations she had typical biochemical features of VDDR- Type-1. Genetic studies revealed the mutation in CYP27B1 gene, confirming the diagnosis of VDDR-type 1 rickets. She was treated with alpha calcitriol and calcium supplements with improvement in her symptoms. **Conclusion:** A novel mutation of the CYP27B1 gene is a rare cause of vitamin dependent rickets. It may be confused with vitamin D deficiency rickets or hypophosphetemic rickets and treated inappropriately. If biochemical investigations and typical radiological features suggestive of genetic errors of vitamin D metabolism, should be investigated for rare genetic errors of vitamin D metabolism by appropriate genetic studies for correct diagnosis and treatment.

KEYWORDS: 1, 25 Dihydroxyvitamin D3, Vitamin D dependent rickets type 1, CYP27B1 gene mutation.

CASE PRESENTATION

A 22 year Saudi woman had history of difficulty in walking, waddling gait and bending of her legs at the age of 4 years. She was diagnosed to have rickets and treated in different hospital with vitamin D and calcium supplements. The symptoms persisted and she was referred to our endocrine clinic for further management. There had no history of fractures, seizures. Her parents were first degree cousins and all her siblings were healthy and did not have similar illness or any known metabolic bone diseases.

Physical examination revealed short stature, height falling below 3rd percentile. No focal dysmorphic features, alopecia, abnormal teeth, reduced muscle tone. There was bowing deformity of distal arms and legs. Gait was waddling. She was pubertal with tanner stage IV. Rest of the physical examination was normal. The laboratory investigation showed normal complete blood count, renal profile and liver profile and the details of the metabolic bone profile was given in Table no:1. The radiological work up showed deformities in radius and ulna and both tibia and pelvis typical of rickets (Fig:1,2)

Based on physical, biochemical, and radiological features genetic type of rickets was suspected. The genetic analysis was performed which revealed mutation in gene CYP27B1 confirming the diagnosis of VDDR-1. She required high doses of calcitriol and calcium supplements to normalize the serum calcium phosphate and PTH levels and relief from symptoms and improvement in radiological features (Fig.3).

Table no.1: Results of bone profile.

S.No	Parameter	Value	Normal range
1	Serum total calcium	1.74	2.1-2.5 mmol/l
2	Serum albumin	44	35-52 g/l
3	Serum alkaline phosphate	628	145-320 iu/l

4	Serum Phosphate	0.54	1.45-1.78 mmol/l
5	Serum Magnesium	0.96	0.65-1.05 mmol/l
6	25-OH cholecalciferol	57	19-127 nmol/l
7	1,25 dihydroxy cholecalciferol	31	41-127 pmol/l
8	Serum creatinine	22	18-26 micromol/l
9	Parathyroid harmone(PTH)	45	1.6-6.9 pmol/l

DISCUSSION

Vitamin D production in the skin under the influence of sunlight is maximized at levels of sunlight exposure that don't burn the skin. Further metabolism of vitamin D to its major circulating form 25 Hydroxy vitamin D (25(OH)D) and hormonal form (1.25(OH)2D) takes place mainly in liver and kidneys respectively. The first step occurs in the liver, where vitamin D hydroxylated to 25(OH) D by 25.[1] hepatic hydroxylase. At least three enzymes have 25- hydroxylase activity: Mitochondrial CYP27A1, microsomal CYP3A4, and CYP2R1.[2] FGF23, calcium and phosphate are major regulators of the renal 1-hydroxylase. The major enzyme that catabolizes 25(OH) D is 24 –hydroxylase. Like the 1-hydroxylase it is tightly controlled in the kidney in a manner opposite to that of the 1-hydoxylase.Vitamin D and its metabolites are carried in the blood bound to vitamin D binding protein (DBP) and albumin. For most tissues it is the free metabolite enters the cell, except kidney and parathyroid glands. Most but not all actions of 1, 25 (OH) 2D are mediated by vitamin D receptor (VDR). VDR is found in most cells resulting in wide spread actions on most physiological and pathological processes. Vitamin D deficiency is the commonest cause of rickets worldwide.[3,4] Uncommon cause of rickets are liver and kidney diseases affecting the Vitamin D metabolism and leading to vitamin D deficiency and rickets.[4,5] Genetic errors of Vitamin D metabolism are rare causes of rickets. Three rare genetic errors of vitamin D rickets were described in the literature.[3,4] The first one involves 1α-hydroxylase deficiency, and also described as Vitamin D dependent rickets Type 1(VDDR-1). Defective vitamin D receptor (VDR) resulting in vitamin D resistant rickets (VDDR) is the second genetic error of vitamin D metabolism. It's also known as Vitamin D dependent rickets Type II (VDDRII). The last and more rare, 25 hydroxy vitamin D3 (25OHD3) deficiency has been reported and linked to a selective mutation in CYP2R1 gene that leads to 25-hydroxylase deficiency.CYP27B1 gene is located on chromosome 12q13. 3 it encodes 1α-hydroxylase enzyme that is localized to the inner mitochondrial membrane of renal cell in which it activates 25OHD3 to synthesize25 OH2D3 to 1, 25 OH2D3. Vitamin D3 binds to VDR and regulates calcium metabolism.[6] Gene alteration CYP27B1 leads to VDDR-1 also called psudovitamin D deficiency reckets. Its an autosomal recessive disorder. So far at least 36 mutations in 54 patients reported from different ethnic groups reported.[7-10] Children with VDDR-1 may present with hypotonia, muscle weakness, joint pain, or fractures in early infancy.[3] Typical laboratory findings such as hypocalcemia, elevated PTH, and low serum 1, 25 (OH)2D, despite normal or elevated 25(OH)D.[11] Radiological features of fractures are evident usually. The clinical presentation of these patients could lead to a wrong diagnosis hypophosphetemic rickets leading to inappropriate treatment and progression of the disease. The demonstration of low levels of 1, 25(OH)2D and high PTH confirms the diagnosis. In our patient presently reported 22year lady since childhood diagnosed to have vitamin D deficiency rickets and was taking vitamin D and calcium supplements. As patient remained symptomatic and disease progressing she was referred to endocrinology department for further evaluation and management. The clinical findings and radiological features were typical for rickets. The biochemical investigations showed low serum calcium and phosphate, high PTH, high alkaline phosphatase, normal serum 25 OH D3 and low normal 1,25 (OH)2D3 suggesting 1α-Hydraxylation defect (Table:1) Subsequent genetic studies identified novel CYP27B1 alteration confirming the diagnosis of VDDR-1 in our patient.VDDR-1 patients show good response to treatment with alfacalcidol or calcitriol (10-400 ng/kg/day).[12,13] Our patient was started on calcitriol and calcium suppliments. Her symptoms muscle aches and joint pains improved and biochemically her serum calcium, serum phosphate and PTH normalized.

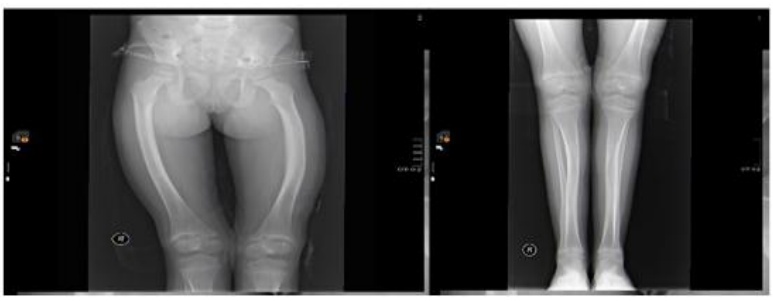

Fig 1: Evidence of bowing of both femurs and tibias
cupping, frying, irregular and broadening of the metphyseal end plates of both tibia and femurs.

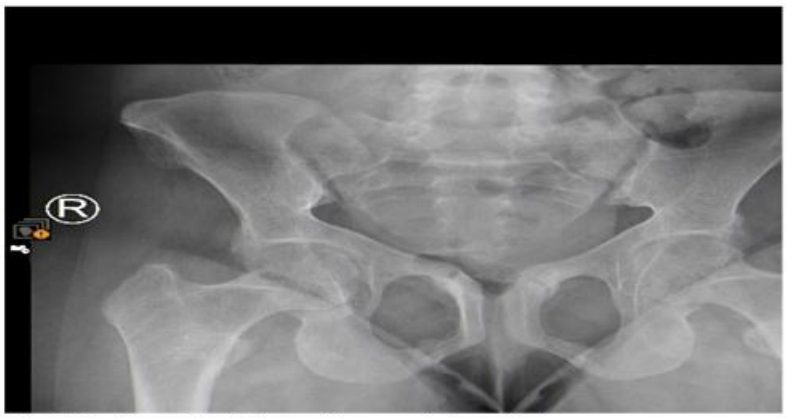

Fig 2: Radiograph of the pelvis revealed multiple pseudofractures/looser zones involving superior and inferior rami bilaterally

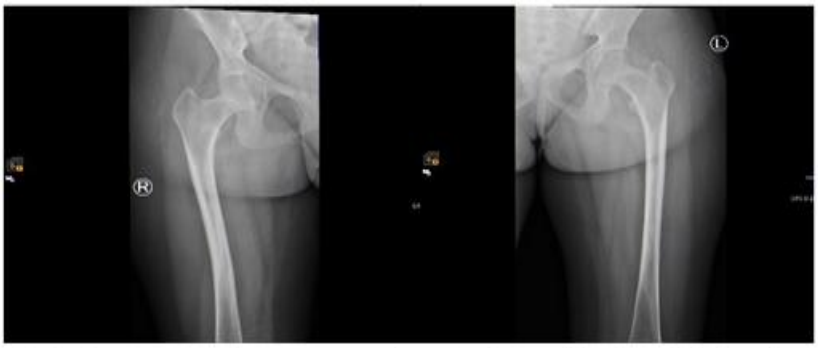

Fig 3 :After treatment improvement of previously noted bowing of fibula and tibia

CONCLUSION

VDDR-1 rickets is the rare cause of rickets. It may be confused with Vitamin D deficiency rickets or hypophosphetemic rickets and treated inappropriately. The typical biochemical abnormal features should be helpful to diagnose VDDR-1 and confirmed by the genetic tests of this rare cause of rickets.

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