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Vitamin D-Dependent Rickets Type 2: Rare Case Report

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Abstract: Vitamin D dependent rickets type 2 A (VDDR2A) is a rare autosomal recessive disorder due to end-organ resistance to 1, 25 $(OH)_2$ vitamin D3. Clinically it can emerged by growth retardation. Rickets in the first year of life is frequently associated with alopecia, hypocalcaemia, secondary hyperparathyroidism. We report a rare case of VDDR2A in a 2 years old boy presenting with failure to thrive, developmental delay, bilateral femoral fractures and prolonged QT interval on EKG. The patient was lethargic, hypoactive, with dysmorphic features, triangular facies, defective dentition, short dysmorphic bowing lower limbs. Laboratory workup showed hypocalcemia, hypophosphatemia with high PTH level and high alkaline phosphatase level. Insuficient vitamin D2-D3 level was found. The diagnosis was confirmed on whole exome sequencing. A wide range of clinical features exists in VDDR type Π. The treatment of the patient with high doses of intravenous and oral calcium, phosphorus and vitamin D gave a slow and a minimal response. In order to achieve a disease control, treatment should be started early in the course of the disease. High doses of intravenous and oral calcium infusions are needed for a good response. However, long term administration of calcium results in complications such as cardiac arrhythmia, hypercalceuria, nephrocalcinosis.

Keywords: Rickets, VDDR2A, Autosomal Recessive, Vitamin D, Calcium, 1,25$(OH)_2$ Vit D3

1. Introduction

Rickets is a bone disease characterized by defective mineralization of growth plate secondary to decreased calcium, phosphorus levels, deficiency of vitamin D and also decreased activity of alkaline phosphate. [1]

The main known types are calcipenic and phosphopenic rickets, but genetics play a role in 13% of cases resulting in a vitamin D hereditary dependent rickets form. It is further classified into types 1A, 1B, 2A, 2B. [1]

Particularly, VDDR2 (vitamin D dependent Rickets type 2), also known as HVDRR (hereditary vitamin D resistant Rickets is a rare autosomal recessive disorder. [1-6] It is caused by mutations in vitamin D receptor gene (50 mutations noted till date), encoded by chromosome 12q12-q14, leading to end-organ resistance to 1, 25 $(OH)_2$ vitamin D3; thus a poor response to vitamin D supplementation. [2-7]

A typical presentation consists of early onset rickets, growth retardation, hypocalcaemia, high 1, 25$(OH)_2$ level, secondary hyperparathyroidism with or without alopecia. [2-6]

Treating patients with higher doses of vitamin D, IV calcium and calcitriol is recommended. [5, 7]

Till date, 11 pediatric cases of VDDR2 were reported in the literature. [1-8] We report here a rare case of VDDR2A in a 2 years old boy presenting with failure to thrive, severe hypocalcemia, bilateral humeral and femoral fractures.

2. Case Report

A 2 years old boy, born by C-section from non-consanguineous parents, at term, with previous ICN admission for neonatal sepsis, and a history of recurrent pulmonary infections presented to the hospital for failure to thrive, hypocalcaemia, bilateral femoral fractures,

neurodevelopmental delay.

At presentation, the patient was lethargic, hypoactive, with dysmorphic features, triangular facies, defective dentition, short dysmorphic bowing lower limbs. There was no blue sclera.

Motor power in all extremities was less than 3. Otherwise, the neurologic exam was normal.

His current weight was 7,5 kg, head circumference was 47.5 and height =71 cm corresponding to -3SD (standard deviation) on growth chart.

Vital signs were within normal range.

Primary investigations were within normal limits including CBCD (Hemoglobin =13.9 g/dl, Platelets=392000, White blood cells =14800), creatinine, CRP, transaminases, lipase, PT, PTT, albumin and urine analysis.

Electrolytes were normal except for hypocalcaemia (Ca++=7.29), hypophosphatemia (Phosphorus= 2.81). In addition, labs showed hyperparathyroidism (PTH level = 310.6) and high Alkaline phosphatase level (1991). Insufficient vitamin D2-D3 level was found (21.81) but 1.25(OH) vitamin D was not available in our laboratory.

Urine spot for Calcium was low<0.8 mg/dl, urine creatinine =20.61 mg/dl and urine phosphorus=54.7mg/dl, thus eliminating the presence of renal tubular acidosis and hypophosphatemic rickets.

Cortisol level (511 nmol/l) and ACTH level (16.7 pg/ml) were normal eliminating the presence of Cushing syndrome as cause of hypophosphatemia.

Antitransglutaminases were negative with normal level of IgG (3.8 AU/ml) and IgA level <3; ruling out the presence of celiac disease and autoimmune disorders.

Given the child's history of recurrent respiratory infections associated with failure to thrive, a sweat chloride test was done to rule out cystic fibrosis which turned out to be negative.

EKG showed QT prolongation (QTc =600ms) and the echocardiogram was normal.

A large skull diameter was noted on skull X-ray but no evidence of skull fracture or craniosynostosis. (Figure 1)

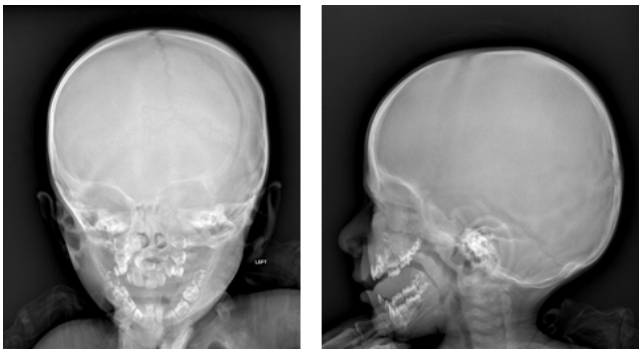

Figure 1. *Skull X-ray showing a large skull diameter.*

X-rays of forearm, arm and leg were remarkable for a fibrillary aspect, periosteal apposition and demineralization of bones. Also, genu varum, convexity of the legs, bilateral femoral and humeral fractures, widening of shoulder joints, scoliosis, fraying of metaphysis of elbow were found on skeletal X-rays. (Figure 2 and figure 3)

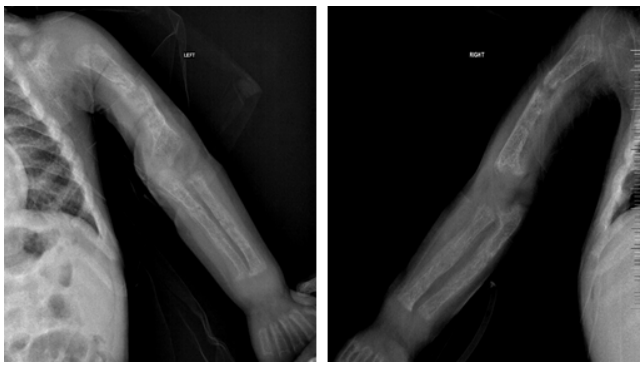

Figure 2. *Upper extremities X-ray showing fibrillary aspect, periosteal apposition and demineralization of bones.*

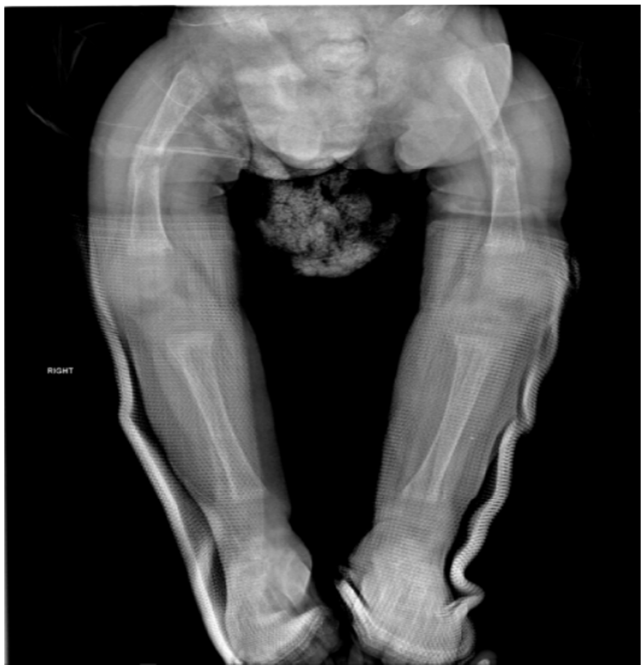

Figure 3. *Lower extremities X-ray showing a genu varum with convexity of the legs and bilateral femoral shaft fractures.*

Treatment with high doses of intravenous and oral calcium, phosphorus and Vitamin D was given with minimal and slow response.

After stabilization of the patient and normalization of calcium level, the patient was discharged on cholecalciferol and calcium gluconate PO.

Whole exome sequencing showed a pathogenic variant in the VDR gene at the homozygous state on chromosome 12q confirming the diagnosis of vitamin D Dependent Rickets type 2A (VDDR2A).

3. Discussion

Vitamin D deficient rickets is a common nutritional disease in infants and children, and can be easily diagnosed and treated by oral or parenteral Vitamin D supplementation. On the other hand, Vitamin D-resistant rickets is a very rare

disorder characterized by resistance to traditional therapeutic regimens that appear in several different phenotypes, heterogeneous pathogenesis, and clinical features. [6]

VDDRII is an extremely rare disorder caused by target organ resistance to 1,25 $(OH)_2$ Vitamin D3, the biologically active form of Vitamin D. It is diagnosed through the finding of normal or elevated circulating levels of 1, 25$(OH)_2$ Vitamin D3, which can differentiate it from Vitamin D-dependent rickets type I (VDDR I). [2] However, we could not measure 1, 25$(OH)_2$ Vitamin D3 Levels. For the confirmation of the diagnosis, molecular testing showed that a pathogenic variant was identified in the VDR gene at the homozygous state: VDR: p. His447Pro.

A wide range of clinical features exists in VDDR type II. These include the variable response to therapy with Vitamin D derivatives and the presence or absence of alopecia. [9]

One of the very common clinical characteristic in cases with Vitamin D-dependent rickets type II is alopecia. [2] It may be present at birth or within the first few months of life. Alopecia is generally not responsive to treatment. [10] The authors Nina et al, Balsan S et al, Feldman D et al registered in their cases the existence of partial alopecia, whereas the author Stojanov presented one case suffering from total alopecia. Some investigators associated the development of alopecia with a more profound 1,25$(OH)_2$ Vitamin D3 resistance. [7, 11-14] However, our 2 years old boy did not present with alopecia but still he had profound 1,25$(OH)_2$ Vitamin D3 resistance.

Radiographic changes and clinical manifestation in bones (bilateral femoral and humeral fractures, widening of shoulder joints, scoliosis, fraying of metaphysis of elbow) were characteristic of rickets in our case. Identical changes in bones are also present in case with vitamin D deficiency rickets, but they disappear with therapeutic dosage of vitamin D (5000 IU/per day) during the time period of 3-5 weeks. [15] On the other hand, in our case, the bony changes started to disappear after three and half months of treatment with high dosages of calcitriol and calcium. This was seen when the values of calcium and alkaline phosphatase were brought to normal.

Slow disappearance of radiological changes in bones in line with normalization of other laboratory findings is in favor of diagnosis of vitamin D –dependent rickets type II.

Clinical features include retarded growth, short stature and bone defects, leading to body deformities, bowing of legs, muscle weakness.

To our knowledge, oral manifestations in VDDR2 were reported only by few authors. Zambrano M et al, Souza AP et al described oral findings as enamel hypoplasia, dentin defects and dental abnormalities and carious teeth. [16-17] The present case reported the same findings of oral manifestations.

The use of intravenous high-dose calcium infusions followed by a high dose of oral calcium is an effective method of treatment of VDDRII. The treatment is more effective if started early in the course of the disease and leads to early healing and better growth with prevention of bone deformities. [2] We manage our patient with oral calcitriol (2 μg/kg/day in two divided doses) and supplemental calcium (3 g/day). High doses of calcium give good response. However, complications such as cardiac arrhythmia, hypercalciuria, and nephrocalcinosis are associated with long term administration of calcium. [18]

4. Conclusion

Calcium and phosphate metabolism play a major role in bone mineralization, regulated by parathyroid hormone and 1,25$(OH)_2$D. 13% of total rickets are due to Vitamin-D dependent rickets, which is hereditary in origin. Early diagnosis and prompt treatment corrects the disturbed bone metabolism, improves the quality of life and protect from fatal cardiac arrhythmia.

References

[1] Thakur M. Familial Vitamin D-dependent rickets Type 2A: A report of two cases with alopecia and oral manifestations. J Oral Maxillofac Pathol. 2019 Feb; 23 (Suppl 1): 130-133. doi: 10.4103/jomfp.JOMFP_309_18. PMID: 30967742; PMCID: PMC6421925.

[2] Inamdar P., Bellad R., Herekar V. Vitamin D-dependent rickets type 2: alopecia responding to 1,25 hydroxy vitamin D. Journal of the Scientific Society. 2016; 43 (3): 155–157. doi: 10.4103/0974-5009.190548.

[3] Azemi M, Berisha M, Ismaili-Jaha V, et al. Vitamin D - Dependent Rickets, Type II Case Report. Mater Sociomed. 2014; 26 (1): 68-70. doi: 10.5455/msm.2014.26.68-70.

[4] Vupperla D, Lunge SB, Elaprolu P. Vitamin D-Dependent Rickets Type II with Alopecia: A Rare Case Report. Indian J Dermatol. 2018 Mar-Apr; 63 (2): 176-179. doi: 10.4103/ijd.IJD_434_17. PMID: 29692463; PMCID: PMC5903051.

[5] Soni SS, Adikey GK, Raman AS. Vitamin D dependent rickets type II: late onset of disease and response to high doses of vitamin D. Saudi J Kidney Dis Transpl. 2008 Sep; 19 (5): 796-8. PMID: 18711299.

[6] Shafeghati Y, Momenin N, Esfahani T, Reyniers E, Wuyts W. Vitamin D-dependent rickets type II: report of a novel mutation in the vitamin D receptor gene. Arch Iran Med. 2008 May; 11 (3): 330-4. PMID: 18426327.

[7] Badabagni, Raghava, Bodduluri, Rambabu, AND Raju, P. V.. "A rare case of Vitamin D dependent rickets type II: a case report" International Journal of Contemporary Pediatrics [Online], Volume 6 Number 5 (23 August 2019).

[8] Cockerill FJ, Hawa NS, Yousaf N, Hewison M, O'Riordan JL, Farrow SM. Mutations in the vitamin D receptor gene in three kindreds associated with hereditary vitamin D resistant rickets. J Clin Endocrinol Metab. 1997 Sep; 82 (9): 3156-60. doi: 10.1210/jcem.82.9.4243. PMID: 9284761.

[9] Takeda E, Kuroda Y, Saijo T, Naito E, Yokota I, Myao M. 1-alpha-hydroxyvitamin D3 treatment of three patients with 1,25-dihydroxyvitaminD3 receptor defect rickets and alopecia. Pediatrics. 1987; 80: 97-101.

[10] Malloy PJ, Hochberg Z, Tiosano D, Pike JW, Hughes MR, Feldman D. The molecular basis of hereditary 1,25-dihydroxyvitamin D3 resistant rickets in seven related families. J Clin Invest 1990; 86: 2071-9.

[11] Nina SMA, Malloy PJ, Pisit P, Dreimane D, Gefner M, Feldman D. Hereditary vitamin D Resistant Rickets. Bone. 2009; 45 (4): 743-746.

[12] Balsan S, Garabedian M, Liberman UA, Eil C, Bourdeau A, Guillozo H, et al. Rickets and alopecia with resistance to 1,25-dihydroxyvitamin D; two different clinical courses with two different cellular defects. J Clin Endocrinol Metab. 1983; 57: 803-811.

[13] Feldman D, Chen T, Cone C, Hirst M, Shani S, Benderli A, Hochberg Z. Vitamin D resistant rickets with alopecia: cultured skin fibriblasts exhibit defective cytoplasmic receptors and unresponsiveness to 1,25 $(OH)_2$ D3. J ClinEndocrinol Met. 1992; 55: 1020-1022.

[14] Stojanov Lj, Vulović D. Sindrom vitamin D rezistentnog rahitisa. Rahitis danas, Niš 1985: 151-159.

[15] Thandrayen K and Pettifor JM. The roles of vitamin D and dietary calcium in nutritional rickets. Bone Rep. 2018; 8: 81-89.

[16] Zambrano M, Nikitakis NG, Sanchez-Quevedo MC, Sauk JJ, Sedano H, Rivera H, et al. Oral and dental manifestations of Vitamin D-dependent rickets type I: Report of a pediatric case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 95: 705-9.

[17] Souza AP, Kobayashi TY, Lourenço Neto N, Silva SM, Machado MA, Oliveira TM, et al. Dental manifestations of patient with vitamin D-resistant rickets. J Appl Oral Sci 2013; 21: 601-6.

[18] Kaptein S, Risselada AJ, Boerma EC, Egbers PH, Nieboer P. Lifethreatening complications of vitamin D intoxication due to overthe-counter supplements. Clin Toxicol (Phila). 2010; 48: 460-462.