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CASE REPORT

Case report: vitamin d-dependent rickets, type 1A

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Abstract

Vitamin D-dependent rickets type 1A is an inborn error of metabolism that affects the action of the 1-alpha-hydroxylase, an enzyme responsible for converting 25-hydroxyvitamin D3 into 1,25-dihydroxyvitamin D3, which is the active metabolite of vitamin D. This report describes the case of a boy who underwent investigation at the age of 20 months due to low weight gain and a history of regression of motor development that had occurred at the age of 9 months, which were associated with generalized hypotonia and bone deformities in the limbs and spine. The patient presented with hypocalcemia, hypophosphatemia, and elevated levels of parathyroid hormone (PTH) and alkaline phosphatase but normal levels of 25-hydroxyvitamin D3, along with an X-ray of long bones suggestive of rickets. He was admitted to the hospital and started on calcium, phosphorus, cholecalciferol, and calcitriol replacement, progressing with clinical and laboratory improvement. Genomic analysis was compatible with vitamin D-dependent type 1 rickets. The patient is currently 5 years and 2 months old and undergoes regular follow-ups with an endocrinologist, maintaining adequate weight gain and motor, neurological, and psychological development. Due to the rare condition of the disease, diagnosis is often delayed. When diagnosed early, prompt treatment substantially reduces the morbidity and complications caused by the disease.

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INTRODUCTION

Rickets is a pathology characterized by impaired mineralization of the bone matrix during the growth phase, and affects both the epiphyseal plate, the trabecular and cortical bones. Its main etiology is the reduction in vitamin D and calcium supply, necessary for adequate bone mineralization, caused by nutritional deficiency or short sun exposure. Other causes are phosphorus deficiency, chronic gastrointestinal diseases that alter nutrient absorption, kidney disease, use of drugs such as barbiturates and changes in vitamin D metabolism[1-3].

Vitamin D-dependent rickets type 1A (OMIM 264700) is a pathology with a prevalence of approximately 1–5/10,000, most common in the Saguenay region of Canada. It is an inborn error of metabolism that alters the 1-alpha-hydroxylase enzyme action. This enzyme is responsible for converting 25-hydroxyvitamin D3 into 1,25-dihydroxyvitamin D3, the active metabolite of vitamin D. Clinical manifestations usually begin between 6 months and 2 years of life. There is delayed motor development, muscle weakness, bone deformities and, in severe cases, seizures due to hypocalcemia. The most common radiological findings are growth plate enlargements and metaphyseal wear. Laboratory tests show increased alkaline phosphatase and parathyroid hormone (PTH), normal or low serum calcium and hypophosphatemia. The dosage of 25-hydroxyvitamin D3 is usually normal, however, the levels of 1,25-dihydroxyvitamin D3 are low[4,5].

Since this is a rare disease, reaching a final diagnosis can be complex. When faced with rickets resistant to vitamin D replacement, the hypothesis of vitamin D-dependent rickets type 1A should be considered and specific treatment should be initiated.

CASE REPORT

A male patient came to the gastroenterology office at 20 months of age, for investigation of low weight gain. The patient had no prenatal or neonatal complications, comorbidities and previous hospitalizations. The only child of non-consanguineous parents; had no family history of skeletal diseases. This patient had enjoyed adequate development until 9 months of age, when he stopped walking and crawling. Upon physical examination, we noticed pain when sitting, generalized hypotonia, inadequate weight gain, widening of the wrists and ankles, arching of the upper and lower limbs and Harrison's sulcus. Laboratory tests showed hypocalcemia, hypophosphatemia, elevated PTH and alkaline phosphatase, anemia and thrombocytopenia, without changes to the 25-hydroxyvitamin D3 (table 1). Hospitalization was decided and calcium, phosphorus, cholecalciferol and calcitriol replacement was started. The calcitriol dose was adjusted according to laboratory test results, with a maximum dose of 4.5mcg/day. Bone inventory with enlargement of the costal ends, long bones with reduced bone density, metaphyseal wear, insufficiency fractures in the fibular shafts (Figure 1). A bone marrow biopsy was performed due to bicytopenia with a diagnosis of myelofibrosis secondary to rickets.

Molecular analysis with genetic sequencing for skeletal diseases identified two heterozygous variants in the CYP27B1 gene (c.1226C>T - p.Thr409Ilee c.1319_1325dupCCCACCC - p.Phe443Profs*24) that cause type 1A vitamin D-dependent rickets (OMIM # 264700). No genetic analysis was performed on the family members.

The patient evolved with clinical improvement and gradual reduction in PTH and ion normalizaton. Currently, the patient, aged 5 years and 2 months, has regular follow-up with an endocrinologist, uses calcium and elemental phosphorus, calcitriol 128 ng/kg/day and cholecalciferol 2000 IU/day,

Table 1. Clinical and laboratory parameters before and after starting treatment with Calcitriol.

Parameters	*Before treatment*	*7 months of treatment*	*Reference value*
Weight	7.9 kg (scores Z -3)	10.1 kg (scores Z -2)	-
Hemoglobin	7.9 g%	11.1g%	11 - 15 g%
Hematocrit	25.6%	34.6%	32 - 42%
Platelets	121000	261000	170000 - 440000
Calcium ion	0.9 mmol/L	1.22 mmol/L	1.12 - 1.32 mmol/L
Serum phosphorus	2.2 mg/dl	4.34 mg/dl	4 - 7 mg/dl
PHT	458 pg/ml	140 pg/ml	12 - 72 pg/ml
Alkaline phosphatase	3375 U/L	934 U/L	4 - 345 U/L
25-OH vitamin D	48.5 ng/ml	80.1 ng/ml	>20 ng/ml
*1,25-OH vitamin D**	-	67.1 pg/ml	19.9 - 79.3 pg/ml

Legend: PTH- Parathormone *1,25-OH Vitamin D was measured only after starting treatment using the Chemiluminescence method.



Figure 1. X-ray of the lower limbs showing reduced bone density and fractures due to insufficiency in the fibular shafts.

maintaining adequate weight gain and neuropsychomotor development and normalization of laboratory and radiological examinations.

DISCUSSION

Type 1A vitamin D-dependent rickets consists of a deficiency of the 1-alpha-hydroxylase enzyme. It is an autosomal recessive disorder, resulting from a mutation in the CYP27B1 gene, located on chromosome 12 (12q131.1-13.3), and identified for the first time in 1961. As a result of this inactivating mutation, 25-hydroxyvitamin D3 is not hydroxylated into 1,25-dihydroxyvitamin D3 and calcium absorption is impaired, causing hypocalcemia and compensatory secretion of PTH, leading to urinary excretion of amino acids and phosphate; also, early bone manifestations with skeletal deformations[3].

In the case described, the patient presented two heterozygous variants in the CYP27B1 gene. Even when heterozygous, these variants can be pathogenic and lead to patient involvement, as demonstrated by Kim[4] and Wang[6]. The first study was carried out in Korea and identified that 3 of the 5 patients analyzed had two heterozygous variants in the CYP27B1 gene. In the second, a multicenter study, 10 of the 19 patients analyzed were heterozygous for two gene mutations[4,6].

The bone marrow biopsy of the described patient demonstrated myelofibrosis. This is a rare condition in pediatrics, with an average incidence of 1.5/100,000 and may be primary or secondary to another pathology[7]. The occurrence of myelofibrosis secondary to rickets is a rare and atypical manifestation that can be reversed after treatment of the underlying disease. The main theory that justifies this condition is osteosclerosis of the bone marrow cavity due to hyperparathyroidism[8,9].

The diagnosis of type 1A vitamin D-dependent rickets is based on biochemical and radiological findings, but it is only confirmed through DNA analysis, with evidence of a mutation in the CYP27B1 gene; however, one should not wait for the results of these tests to start treatment[5,10]. Ionic disorders must be promptly corrected due to the risks of tetany and seizures found in this pathology. Specific treatment consists of chronic 1,25-dihydroxyvitamin D3 replacement therapy. The dose depends on the severity of the disease and the child's body weight, and must be modified according to the results of biochemical analysis. Chronic treatment aims to maintain the patient in normocalcemia without hypercalciuria, with normal PTH levels, resulting in increased muscle strength and resolution of bone lesions, allowing the child to grow normally. It is important to maintain adequate dietary calcium intake[11,12].

During the initial phase of treatment, strict supervision is necessary, with clinical assessments and laboratory measurements, including calcium, phosphorus, alkaline phosphatase and PTH, every two to three weeks. After four weeks of therapy, an evident improvement on the radiograph is expected, which should be repeated after three months, when the growth plates should have regained a normal appearance. Patients may be evaluated at three-month intervals during maintenance therapy. Hand x-rays are performed once a year to check for the reappearance of rachitic changes[11-13].

During therapy, side effects such as hypercalcemia, hypercalciuria, nephrocalcinosis and intraocular calcifications may be observed, making renal monitoring important at each visit, in addition to annual renal ultrasound. Ophthalmological consultation and slit lamp examination should be considered if manifestations of chronic hypercalcemia, such as nephrocalcinosis, are evident[11-13].

CONCLUSION

Given the case presented, although deficient rickets is still prevalent in Brazil, as reported by Ferreira[14], it is important to consider other rare forms, such as vitamin D-dependent rickets type 1A, in the differential diagnosis. Early diagnosis and appropriate treatment significantly reduce morbidity and complications caused by the disease.

REFERENCES

1. Bueno AL, Czepielewski MA. A importância do consumo de cálcio e vitamina D no crescimento. J Pediatr. 2008; 84(5).
2. DeLuca HF, Schnoes HK. Metabolism and mechanism of action of vitamin D. Annu Rev Biochem. 1976; 45: 631
3. Haffner D, Lifheit-Nestler M, Grund A, Schnabel D. Rickets guidance: part I – diagnostic workup. Pediatr Nephrol. 2022; 37(9): 2013-2036.
4. Kim CJ. Vitamin D dependent rickets type I. Korean J Pediatr. 2021 Feb; 54(2):51-54.
5. Mckusick, VA. Vitamin D hidroxylation-deficient rickets, type 1A [Internet]. OMIM, 2020 [citado em 02 mar 2022]. Disponível em: https://www.omim.org/entry/264700#
6. Wang JT, Lin CJ, Burridge SM, Fu GK, Labuda M, Portale AA, et al. Genetics of vitamin D 1alphahydroxylase deficiency in 17 families. Am J Hum Genet. 1998; 63(6): 1694-1702.
7. Mishra P, Halder R, Aggarwal M, Seth T, Mahapatra M, Pati HP, at al. Pediatric myelofibrosis: WHO 2024 update on myeloproliferative neoplasms calling? Pediatr Blood Cancer. 2020 May;67(5):e28232.
8. Balasubramaian S, Varadharajan R, Ganesh R, Shivbalan SO. Myelofibrosis and vitamin D deficient rickets – a rare association. Indian pediatrics. 2005; 42: 482-484.
9. Kamien B, Harris L. Twin troubles – rickets causing myelofibrosis. J Paediatr Child Health. 2007 Jul-Aug;43(7-8):573-5. doi: 10.1111/j.1440-1754.2007.01143.x
10. Delvin EE, Glorieux FH, Marie PJ, Pettifo JMr. Vitamin D dependency: replacement therapy with calcitriol. J Pediatr. 1981 Jul;99(1):26-34. doi: 10.1016/s0022-3476(81)80952-3
11. Haffner D, Lifheit-Nestler M, Grund A, Schnabel D. Rickets guidance: part II – management. Pediatr Nephrol. 2022; 37(10): 2289-2302.
12. Dhull RS, Jain R, Deepthi B, Cheong HII, Saha A, Mehndiratta M, et al. Raquitismo dependente de vitamina D: tipo 1: serie de casos de dois irmãos com mutação CYP27B1 e revisão da literature. J Bras Nefrol. 2020; 42(4):494-497.
13. Levine MA. Dignosis and management of vitamin D dependent rickets. Front Pediatr. 2020; 8:315.
14. Ferreira FNS, Silva CN, Silva DN, Oliveira ARV, Pádua KMD, Morais EA, et al. Raquitismo carencial: estado de alerta. Resid Pediatr. 2021;11(3):1-3. doi: 10.25060/residpediatr-2021.v11n3-176