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Vitamin D-dependent rickets type II with alopecia: A rare case report

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Abstract
Vitamin D-dependent type two rickets (VDDRII) is a rare autosomal recessive disorder caused by a mutation in the vitamin D receptor gene, leading to end-organ resistance to 1,25(OH)2 vitamin D3. A patient with this condition presents with refractory rickets and growth retardation during the first year of life. It is frequently associated with alopecia totalis. Due to target organ resistance, its response to vitamin D is poor. The recommended treatment is supraphysiological doses of 1, 25(OH)2 vitamin D3 and a high dose of oral or intravenous calcium. The response of alopecia to treatment is generally poor. A case of a 15-month-old female child with VDDRII whose rickets partially responded to 1, 25(OH)2 vitamin D3 but showed poor response of alopecia to the treatment is presented.

Keywords: alopecia, end-organ resistance, vitamin D, 1, 25 (OH) 2 vitamin D3, refractory rickets

Introduction

Vitamin D-dependent rickets (VDDR) type II, also known as hereditary vitamin D-resistant rickets type II (VDDRII), is a rare autosomal recessive disorder caused by a mutation in the vitamin D receptor gene, leading to end-organ resistance to 1,25(OH)2 vitamin D3. A patient with this condition presents with refractory rickets and growth retardation during the first year of life [1]. This condition is frequently associated with alopecia totalis. Biochemical parameters indicative of this condition are hypocalcemia, hypophosphatemia, hyperparathyroidism, and elevated circulating levels of 1,25(OH)2 vitaminD3. The significantly elevated serum levels of 1,25(OH)2 vitamin D3 distinguishes this disorder from 1-α–hydroxylase deficiency, which is associated with low levels of 1,25(OH)2 vitamin D3. Due to target organ resistance, the response to vitamin D of a patient with this condition is poor. The recommended treatment is supraphysiological doses of 1,25(OH)2 vitamin D3 and high doses of oral or intravenous calcium. To date, 50 unique mutations of vitamin D receptor gene have been noted [2].

Case report

A 15-month-old Saudi female was seen in the pediatric clinic at the National Guard Comprehensive Specialized Clinic, Riyadh, Saudi Arabia. She visited the clinic for a routine one-year vaccination. She was the third baby of first cousin parents. A positive family history of hypocalcemia in two cousins but without a clear diagnosis was reported. This particular case was the product of a full-term spontaneous vaginal delivery. Birth weight was 3 kg. The baby demonstrated normal gross motor developmental milestones. She had achieved head control at five months, sitting without support at seven months, and was able to walk alone by 13 months. Her other developmental domains were also normal. On physical examination, the baby's weight was 8 kg (5th percentile based on the World Health Organization (WHO)'s weight for age), her length was 71 cm (< 3rd percentile based on WHO's weight for age), and she had a normal head circumference of 45 cm (10th percentile WHO's head circumference for age). She had alopecia totalis (loss of hair on the scalp and eyelids) as shown in Figure 1. The patient also had evidence of rickets in the form of wide-open anterior fontanel, fronto-parietal bossing, rachitic rosary, Harrison's sulcus, wrist widening, protuberant abdomen, and bowed legs (Figure 1). No evidence of other vitamin or mineral deficiencies was found. Laboratory investigations revealed a hemoglobin of 12.2 gm/dL. Her renal function tests (urea 1.8 mmol/l, serum creatinine 31 mmol/l, sodium 136 mmol/L, potassium 4.1 mmol/L, chloride 107 mmol/L, and venous bicarbonate l 18 mmol/L) were in the normal range, ruling out a renal etiology of rickets. Her serum calcium was 2.29 mmol/L. Serum phosphorus was low (0.83 mmol/l), and high alkaline phosphatase (1775 U/L). X-ray was suggestive of rickets (figure 2), which was further confirmed by increased parathormone levels of 765 pmol/L. Her 25(OH)2 vitamin D3 level was satisfactory (50.1 nmol/l) and 1,25(OH)2 vitamin D3 levels was elevated (446 pmol/L), suggestive of end-organ insensitivity. Genetic testing confirmed the diagnosis of autosomal recessive VDDRIIA. Ultrasound of the kidneys showed grade I bilateral hydronephrosis.

The patient was referred to a pediatric endocrinologist who started the patient on Alfacalcidol drops (1-hydroxycholecalciferol) at dose of 3 µg daily in addition to vitamin D3 (Cholecalciferol) 1000 IU daily and oral calcium gluconate at 1200 g/day. She was also hospitalized and received intravenous calcium. At the 6-month follow-up, the patient showed an improvement in her laboratory findings. The patient was also referred to a pediatric dermatologist who recommended no intervention for the alopecia totalis.

Fig 1: Child presented with aloplecia, frontoparietal bossing, and bowlegs

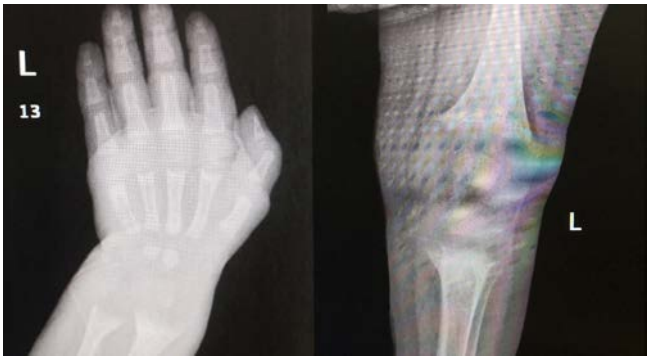

Fig 2: X-rays of wrist and knee showing cupping, flaring, and flaying.

Discussion

When nutritional rickets are detected, other etiologies of rickets are often not considered. This thinking results in the delayed initiation of treatment, resulting in severe growth retardation and deformities. Red flag signs suggesting a non-nutritional etiology are early onset of rickets, severe deformity, deformities localized to lower limbs, associated failure to thrive, acidotic breathing, and the presence of alopecia. This patient had alopecia with severe deformities, aiding the diagnosis of VDDRII.

VDDRII is an extremely rare disorder caused by target organ resistance to 1,25(OH)2 vitamin D, the biologically active form of vitamin D. VDDRII is diagnosed through findings of normal or elevated circulating levels of 1,25(OH)2 vitamin D, which differentiate it from vitamin D-dependent rickets type I (VDDRI). The latter condition is caused by defective 1-α-hydroxylation of 25(OH) vitamin D in the kidneys, resulting in low serum levels of 1,25(OH) vitamin D3[2]. The most common defect is undetectable binding of 1,25(OH)2 vitamin D to the receptor either because of an absent vitamin D receptor (VDR) or a defective steroid-binding domain of the VDR[3]. Patients with VDDRII present with early-onset rickets, hypocalcemia, and associated total body alopecia [4]. The alopecia may be present at birth or within the first few months of life and progresses to aloplecia totalis by childhood. Aloplecia is generally not responsive to treatment [4].

VDDRII with alopecia seems to be particularly common in the Arab populations. Among 30 cases of VDDR II with alopecia reported in the literature, 13 patients were Arab [5]. This result could be due to the higher prevalence of the disease gene in Arabs or may simply be the result of the high prevalence of consanguinity in some Arab communities.

The use of intravenous high-dose calcium infusions followed by a high dose of oral calcium is an effective treatment method for VDDRII. The treatment is more effective if started early during the course of the disease and leads to early healing and better growth with prevention of bone deformities [6].

Conclusion

VDDRII is a rare hereditary autosomal recessive disease originating from heterogenous mutations in the vitamin D receptors. Clinical manifestations are identical to those observe in Vitamin D-deficiency rickets (except alopecia), whereas hypocalcemia and high values of 1.25-dihydroxyvitamin D in serum were characteristic in laboratory findings regarding VDDRII. Treatment is long lasting followed with administration of high doses of calcium and a constant dosage of calcitriol.

Declaration of patient consent

I certify that I have obtained all appropriate patient consent forms. In the form the The patient's parents gave their consent for the images and other clinical information to be reported in the journal.

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