

Vitamin D Dependent Rickets Type II with Alopecia

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ABSTRACT Vitamin D dependent rickets Type II (VDDR II) is a rare form of autosomal recessive disorder, which is inherited and often caused by mutation of a gene on vitamin D receptor which in turn prevents normal physiological response to 1,25(OH)₂ vitamin D. The elevated circulating levels of 1,25-dihydroxyvitamin D₃ is a diagnostic feature of VDDR II, while the presence of alopecia differentiates it from vitamin D-dependent rickets Type I. VDDR II is considered to be the best example of aberrant target tissue response. The researchers thereby report a case of a two-year old female child with short stature, typical features of rickets and lack of hair growth. Upon investigation the level of 1,25(OH)₂D was found to be high which is diagnostic of VDDR type II. The child was started on high dose of calcitriol and oral calcium but on follow-up did not show much improvement probably due to poor compliance.

I. INTRODUCTION

Vitamin D dependent rickets Type II (VDDR II) is a genetically determined rare form of autosomal recessive disorder most often caused by mutation on vitamin D receptor gene preventing normal physiological response to 1,25(OH)₂ vitamin D (Kliegman et al. 2010). The circulating levels of 1,25(OH)₂D are elevated and constitute the hallmark diagnostic lab test (Kliegman et al. 2010). The intriguing disease generally presents with a clinical picture of rickets, hypocalcemia, hypophosphatemia, growth retardation, hyperparathyroidism along with elevated circulating levels of 1,25(OH)₂D (Mishra et al. 1996). In resource poor settings with lack of facilities for estimation of 1,25(OH)₂D and parathyroid hormone, alopecia remains the only clue to the diagnosis of this rare syndrome in association with resistant rickets (Malla et al. 2010). The researchers are reporting a similar case of vitamin D dependent rickets Type II (VDDR II) presenting with alopecia.

II. CASE PRESENTATION

A two-year old female child with short stature and lack of hair growth was brought by her

parents. The child hailed from Hyderabad, capital of Andhra Pradesh which is not an endemic area for fluorosis. Family history revealed that she was born to parents of second degree consanguineous marriage and was third in birth order. Parents and elder two siblings were normal and did not have any history of similar illness. Her personal history depicted that she was developmentally normal, with uneventful prenatal, natal and post natal period. The child had normal teething eruption and her anterior fontanelle was found to be closed.

On examination, she had typical features of rickets with widening of wrist and ankles with anterolateral bowing of legs. Generally evident features of calcium deficient rickets like rachitic rosary, Harrison's groove and profound myopathy were absent. She had short stature; height was 71 cms (< 3rd percentile for age). No abnormality was detected on systemic examination of cardiovascular, respiratory and central nervous system. Alopecia was overtly evident (Fig. 1). The child had previously received multiple injections of vitamin D₃. In view of alopecia, vitamin D dependent rickets Type II was suspected and serum vitamin D levels were estimated.

Upon investigation the level of 25(OH)₂D was found to be > 156 ng/ml (normal 7.6 to 75 ng/ml) while the level of 1,25(OH)₂D was found to be > 545 pg/ml (normal 19.6 to 54.3 pg/ml). Due to the presence of such high levels of circulating 1,25(OH)₂D which is the hallmark of VDDR II, and the clinical clue of alopecia, the diagnosis was confirmed. Further investigations showed a serum calcium level of

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Fig. 1. Photograph of the child showing Alopecia and widening of the wrists

8.1 mg/dl and phosphorous 2.7 mg/dl with markedly raised alkaline phosphatase level of 1650 IU. The serum parathormone level was 365.6 pg/ml (normal: 15-65 pg/ml). X-Ray of wrist revealed metaphyseal widening, flaying and cupping, suggestive of rickets (Fig. 2).

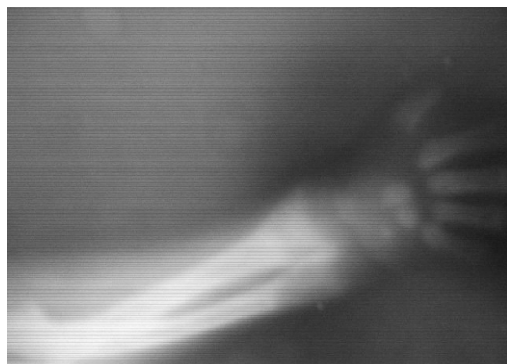


Fig. 2. X-ray of wrist showing widening, flaying and cupping at the lower end of radius and ulna

As high doses of calcitriol and calcium much above the daily requirements are used in such cases the child was started on calcitriol (8 capsules of 0.25 micrograms each – total 2 micrograms) and 2000 mg per day of oral calcium. But due to the financial constraints of parents, only two capsules of calcitriol per day were actually administered to the child. After six months of follow-up, the researchers observed that the physical, biochemical and radiological features

of rickets were still persistent with a sparse hair growth on the scalp.

III. DISCUSSION

Hereditary 1, 25-dihydroxy vitamin D resistant rickets (HVDDR), also known as vitamin D dependent rickets type II is a rare autosomal recessive disease that arises as a result of mutations in the gene encoding the vitamin D receptor (VDR). The disease presents itself with rachitic changes, unresponsiveness to vitamin D treatment with elevated circulating levels of 1,25-dihydroxyvitamin D₃ (Kliegman et al. 2011). Vitamin D dependent rickets Type II is one of the best examples of aberrant target tissue response. There are two types of vitamin D dependent (hereditary) rickets (VDDR) known till date, Type-I and Type-II. Type-I is caused by mutation in the gene encoding 1-alpha-hydroxylase while Type-II is caused by mutation in the VDR (Vitamin D Receptor) gene. Both forms of the diseases display an autosomal recessive trait.

VDDR-II consists of a spectrum of intracellular vitamin D receptor (VDR) defects and is characterized by the early onset of severe rickets and associated alopecia. The cause of alopecia is postulated to be the lack of ligand-independent function of the vitamin D receptor in keratinocytes which is necessary for proper anagen initiation (Sakai et al. 2001). Children with this type of rickets typically present with bowing of lower extremities related to weight bearing at the age of walking and short stature. Rachitic rosary, Harrison's groove, profound myopathy, which are characteristic of calcium deficient rickets are not evident (Mishra et al. 1996).

Serum calcium levels in such cases is either normal or low, while phosphorous levels are low and alkaline phosphatase levels are elevated. The levels of 1,25 dihydroxy cholecalciferol are elevated which is considered to be the diagnostic hallmark of this disease (Kliegman et al. 2010). VDDR type II is more often resistant to vitamin D treatment and hence massive doses of 1,25-dihydroxyvitamin D are recommended, but even then response to the treatment is variable. In general, it is observed that cases associated with alopecia as a feature respond poorly to treatment (Mishra et al. 1996). Though the exact incidence is not known, this is a rare form of the disease.

On review of literature, a case report revealed two siblings with VDDR II with alopecia reported by Takeda et al. (1989) who responded to treatment with 50,000 IU of Vitamin D2, daily for 2 years without any recurrence for 14 years after cessation of therapy.

A similar case study by Wong and Leung (2008) reported a case of an 8 year old girl with VDDR II who responded to high doses of oral calcium. Lin and Uttley (1993) reported a 5 year old child with VDDR type II with unresponsiveness to high doses of vitamin D and oral calcium who responded completely to intra arterial infusion of calcium for 1 year. A case of a child with alopecia who did not respond to both high dose calcium and vitamin D was also reported by Fraher et al. (1986).

Very few such case reports were found in the Indian literature. Mishra et al. (1996) reported a case of VDDR II without alopecia who responded to high dose calcium after five months of treatment. Bajpai et al. (2005) have reported in their analysis about a series of 131 cases of non-azotemic refractory rickets of which 19.6% were due to VDDR; however, none of the cases reported were having alopecia. Further, the study did not differentiate between Type I and Type II VDDR since the vitamin D levels were not measured.

In addition to typical biochemical features of rickets (Hypocalcemia, hypophosphatemia, high levels of alkaline phosphatase and parathormone), high levels of 1,25(OH)₂D₃ were reported in VDDR II by Kruse and Feldmann (1995). In this case the child also had high circulating levels of 25(OH)D₃ which could be the result of multiple injections of vitamin D₃ that the child had received initially. The 25-hydroxylation of vitamin D₃ is poorly regulated, leading to a conversion of almost all vitamin D₃

present into 25-hydroxyvitamin D₃ (25(OH)D₃) (Mathieu et al. 2007). This case is being reported due to its rarity and to create awareness among the clinicians to think of VDDR type II whenever Rickets is associated with alopecia totalis.

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