Case Reports

Vitamin-D Dependent Rickets Type II

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Vitamin-D dependent rickets type II (VDDRII) or hereditary 1,25-dihydroxy vitamin D_3 resistant rickets is an autosomal recessive inheritable disorder, resulting from a failure of target organs to respond to hormonal form of vitamin D *i.e.* 1,25-dihydroxy vitamin D_3 ($1,25(OH)_2D_3$)(1). It is characterised by an early onset refractory rickets, hypocalcemia, hypophosphatemia, growth retardation, hyper-parathyroidism, and elevated circulating levels of 1,25-$(OH)_2D_3$ and frequent unexplained total scalp and body alopecia(l-5). Since the time, Brooks, *et al* reported the first case in 1978(2), just about 30 cases have been reported in the world literature. We report one such case without alopecia.

Case Report

A 3-year-old girl was brought with complaints of widening of wrists and ankles for last *2%* years and waddling gait. There was no history suggestive of malabsorption, oliguria, polyuria, jaundice and intake of drugs, or a similar illness in the family. She was the first child to non-consanguineous marriage. The prenatal, natal and the postnatal periods were uneventful. She was diagnosed as a case of rickets at the age of 1 year 8 months by a private practitioner. The blood levels of calcium, alkaline phosphatase and 24-h urinary calcium were 6.5 mg/dl, 342 IU/L and 2 mg/kg/day respectively. She was treated with an oral dose of 600,000 IU of Vitamin D_3.

Examination at 3 years showed marked widening of wrist and ankles and anterolateral bowing of legs. There was no rachitic rosary, Harrison's sulcus or caput quadratum. The eruption of teeth was normal and the anterior fontanelle had closed. There was no evidence of latent tetany. The scalp and body hair were normal. There was a small perifrenular mucocele at the inner aspect of lower lip. The weight and height were within the 25th to 50th percentile for age. Examination of cardiovascular, respiratory and central nervous system did not reveal any abnormality.

Investigations showed blood level of calcium 7.8 mg/dl (normal 8.5-10.5 mg/dl), phosphorus 3.3 mg/dl (normal 2.7-4.5 mg/dl) and alkaline phosphatase 1000 IU/L (normal 187-518 IU/L) respectively. The X-rays of wrists and knees showed features of active rickets. She was given 600,000 IU of vitamin D_3 along with oral calcium supplementation. She reported six months later with features of rickets still persisting, both clinically and radiologically. The serum biochemistry revealed hypo-calcemia (7.9 mg/dl) and hypo-phosphatemia (2.07 mg/dl). A repeat dose of vitamin D_3 was administered.

Three months later the clinical and radiologic features of rickets persisted. Investigations done showed serum calcium, phosphorus and alkaline phsophatase of 8.6 mg/dl, 2.11 mg/dl and 1168 IU/L respectively. Examination of urine revealed

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a pH of 7.5 specific gravity of 1018 and mild generalised aminoaciduria; there was no glucosuria and albuminuria. The 24 h urinary excretion of calcium and phosphorus was 75 mg (4.7 mg/kg/day) and 306 mg (20.4 mg/kg/day) respectively. The excretion of 24-h fecal fat was normal. The blood levels of protein, sodium, potassium, chloride, creatinine, bilirubin, GOT, GPT, bicarbonate, urea and sugar were normal. The X-rays of wrist and knees showed features of rickets. Ultra-sonography of abdomen did not reveal any abnormality. The serum level by radio-immunoassay, of total parathormone was 120 pg/ml (normal 12-72 pg/ml), 25-hydroxy vitamin D was 48 mg/ml (normal 17-54 mg/ml) and $1,25(OH)_2 D_3$ was 93 pg/ ml (normal 20-76 pg/ml). She was diagnosed as VDDR II. She was treated with monthly injections of 600,000 IU of vitamin D_3 alongwith oral calcium supplementation 800 mg-lg/day. After six months, she showed considerable improvement, clinically, biochemically and radiologically. The waddling gait had disappeared and serum calcium and phosphorus increased to normal levels. The X-ray of wrist showed complete healing while knee showed signs of healing. Stoppage of treatment for 4 months led to reduction in levels of calcium to 4.9 mg/dl and phosphorus 1.8 mg/dl. On restarting treatment the blood levels of calcium and phosphorus returned to normal.

Discussion

The patient was diagnosed as VDDR type II on the basis of high levels of $1,25 (OH)_2D_3$, normal levels of 25-hydroxy vitamin D, hypo-calcemia, hypo-phosphatemia and hyperparathyroidism. The other causes of rickets such as nutritional, malabsorption, drug induced, hepatic, renal and familial hypo-phosphatemic were excluded on clinical and laboratory evaluation. Presence of high levels of $1,25-(OH)_2D_3$ ruled out VDDR type I. Though alopecia totalis is encountered in majority of cases of VDDR type 11(1,3-5), it was not a feature in the present case.

Recent studies indicate the heterogenous nature of the defects leading to VDDR II. The defect could be an absent(6), or a truncated(7) receptor, or a point mutation in the steroid binding domain(8) or in one of the zinc fingers in the DNA binding domain of the receptor(9), or still a defective nuclear localisation of hormone receptor complex(l0).

There is no consensus on the treatment of VDDR type II. Occasional patients respond to high dose of vitamin D_3(2) or a high (11) or low(12) dose of $1,25-(OH)_2D_3$. Even spontaneous healing has been reported(l,4). Lately, high dose calcium therapy has been reported to be most promising^). It is recommended initially intravenously (1.4 g/day) for 2- 3.5 months, followed by weekly infusions and then orally up to 6 g/day. In these patients, biochemical parameters normalised within two months and radiological healing occurred in 3-5 months(13).

The earlier cases reported from India, with alopecia and autosomal recessive mode of inheritance, did not respond to therapy with vitamin D_3 or 1-alpha-hydroxy vitamin D_3(14,15). The present case responded to high doses of vitamin D_3 like that of Brooks, *et al(2).* It is likely that there exists an alternate pathway of action of vitamin D_3 independent of the vitamin D receptor. In some cases of VDDR II, the vitamin D receptor may be partially functional, indicative of a less severe disease which is substantiated by absence of alopecia(ll).

In the present case, it was difficult to

determine the mode of inheritance, since none of the family members in three generations suffered from a similar illness. However, the possibility of a mutation cannot be ruled out.

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