

**HEREDITARY 1,25 - DIHYDROXYVITAMIN D-RESISTANT RICKETS
A REPORT OF SEVERAL CASES IN A KINDRED**

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We report a Bahraini family with five cases of vitamin D resistant rickets and alopecia. Investigation confirmed the diagnosis of hereditary vitamin D resistant rickets, type II in 2 of the siblings who were fully investigated. Although we do not have data to support it, we believe all the sibs had the same type of rickets. *Bahrain Med Bull* 1996;18(1):

Hereditary 1,25-dihydroxyvitamin D resistant rickets (HVDRR), also known as vitamin D-dependent type II rickets, is a rare autosomal recessive disorder¹. It results from defective response of the target tissues to the active hormonal form of vitamin D [1,25 (OH)₂D₃]. The syndrome is characterised clinically by early onset of rickets with hypocalcemia, hypophosphatemia, secondary hyperparathyroidism in the presence of normal or elevated circulating levels of 1,25 (OH)₂D₃. Affected patients in half the kindred's show either partial or total alopecia. The unresponsiveness of the target tissues to 1,25(OH)₂D₃ has been proven to result from mutations in the gene encoding the vitamin D receptor (VDR). These mutations adversely affect the structure and function of VDR for calcitriol.

In this paper we report our findings in 5 siblings from a Bahraini family of consanguineous marriage who presented to us with vitamin D-resistant rickets and alopecia. The clinical picture and the course of the disease were similar in all the siblings. However, since not all these sibs were investigated we have chosen to present the clinical profile of only 2 siblings who were investigated in details. To the best of our knowledge this is the first case of HVDRR from the Arabian Gulf region.

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THE CASE

A Bahraini family of 11 members (5 males, 6 females) 5 of whom had HVDRR. The family pedigree (Fig 1) did not reveal any affected member in the past generations. Table 1 show the biochemical data of the patients. Since not all the patients were investigated we report only the two cases who were investigated. Figure 2 shows patient number 1 who was not investigated presenting with partial alopecia, rickettic broadening of ankles, coxa vara and narrowing of thoracic cage.

Table 1
Biochemical Data of 5 members of the family with HVDRR

Patients with Case No.	S.Cal (8.5-10.5 mg/dl)	S.Phos (2.4-3.4 mg/dl)	Alk Phosp (25-80 iu/L)	pTH (20-90 pmol/L)	1,25 (OH) ₂ D ₃ (16-92 pmol/L)	U.Phos (400-1300 mg/day)	U.Cal (50-250 mg/day)
1. RAA	8.1	1.8	1506	145		196	
2. RiAA	8.5	2.0	195				
3. HAA	7.6	2.2	1184	88	106		
4. HaAA	8.3	1.6	2969	160	>130	50	33
5. RmAA	7.7	2.7	1725				

HAA was born at term in August 1986 weighing 3.600 Kg. Thin, dry wrinkled skin and subtotal alopecia was noted at birth. Liver edge was felt 3 cm below the right costal margin and the spleen was felt 3 cm below the left costal margin. Because of the family history he was investigated for rickets. Skeletal survey did not reveal any evidence of rickets and the blood biochemistry too was normal. By the age of six months, however, he developed physical signs of rickets in the form of broadened wrists, rachitic rosary etc. Blood urea and electrolytes were normal. Results of other laboratory investigations are given in Table 1. Impairment of hearing followed by delayed speech was noted. He was started on one alpha calcidol, but did not show any response. Addition of oral calcium administration was also not helpful. He developed multiple fractures. At the age of 8 years he has severe deformities of the bones, growth retardation and severe enamel hypoplasia.

HaAA a product of term gestation and normal delivery in November 1988 was first referred to our hospital at the age of 13 months for delay in walking and loss of scalp hair. He had had repeated respiratory infections and loss of scalp hair since early infancy.

At presentation his weight was 8.200 Kg. Broad wrists, ankles and genu valgum deformities were noted. X-rays (Fig 3) confirmed florid rickets. Blood urea and electrolytes were within normal limits. Table 1 shows results of other laboratory tests. Parents refused further investigations and the patient was taken home against advice. He was next seen in February 1990. His speech was delayed and was still not able to walk. He had fracture of the left tibia. He was started on calcitriol, but again the parents took him abroad for treatment. He was continued on calcitriol with oral calcium. He did not show any sign of healing of rickets or improvement in his general health. Growth retardation and enamel hypoplasia was striking. He died at the age of 5 years with extensive bronchopneumonia.

DISCUSSION

The diagnosis of HVDRR in 3 siblings (Cases No. 1,2 and 5) is presumptive as our investigation of these patients was incomplete. Nevertheless, all these siblings exhibited the classical clinical picture of HVDRR type II, including early onset of severe rickets, alopecia, depressed levels of serum calcium, phosphorus and failure of response to therapy with vitamin D, one alpha calcidol or calcitriol. Also, parathormone level was elevated in 2 patients (Case No. 1 and 4) and high normal in one case (No.3). Serum calcitriol was high in one case (No. 4) and high normal in another (No.3). Twenty four hours urinary phosphate excretion was low in 2 patients and normal in one. The diagnosis of HVDRR type II in case No.3 and 4 is in our opinion, firmly established.

The occurrence of different types of hereditary rickets in one kindred would be extremely unlikely. Hence we believe that all the sibs had HVDRR type II. HVDRR is a heterogeneous disease resulting from a series of mutations in the VDR gene. Patients with severe receptor negative mutations and truncated VDR have severe course and show no response to therapy. We believe our patients belong to this group.

Since the major effect of 1,25 (OH) 2D3 is enhancement of the intestinal absorption of calcium, some investigators have suggested intravenous administration of large doses of calcium in order to achieve normocalcemia and healing of rickets. Reports of encouraging short term results of high dose intravenous (intracaval) calcium infusion have been published^{4,5}. Normalisation of serum calcium, PTH, phosphorus, alkaline phosphatase values, and alleviation

of bone pain and radiologic evidence of healing of rickets have been reported^{4,5}. However, the administration of large quantities of calcium through an indwelling catheter over an extended period of time is potentially hazardous. Cardiac arrhythmias and recurrent sepsis has been frequently encountered.

CONCLUSION

Hereditary 1,25-Dihydroxyvitamin D-resistant rickets is rare type rickets which can cause severe growth retardation and disability. We have presented this case to highlight the importance of early institution of aggressive therapy.

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