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OSTEOPETROSIS WITH RICKETS IN INFANCY*

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Osteopetrosis is a rare generalized skeletal disorder characterized by increased density of the bones with loss of their normal structure. It was described for the first time by Neuman in 1880. The term osteopetrosis was introduced in 1926 by Karschner. Since then, reports of over 300 cases from different countries have been published[1].

Osteopetrosis may be transmitted in a dominant or recessive form. In both forms there are two varieties: one is benign with late manifestations in which the prognosis is good, the other is malignant beginning with osteosclerosis but complicated by severe anemia[2,3].

The recessive malignant form is the most striking and best-known of the osteopetroses in which parental consanguinity is often demonstrated[2,4] The malignant types of osteopetrosis most commonly seen during childhood are characterized by mental and motor retardation, weakness, hydrocephalus, optic atrophy, poor dentition, progressive enlargement of the spleen, liver and lymph nodes, and a refractory type of anemia[2].

The etiology of osteopetrosis is still unknown. The clinical data strongly suggest that the disease is the result of an inborn error of metabolism, but no biochemical abnormalities have been discovered yet. No disorders closely linked to parathyroid or vitamin D dysfunction have been demonstrated in this disease, whereas rickets in a severe form has been observed repeatedly[1,5-9].

In this report 6 cases with osteopetrosis associated with rickets seen between 1970 and 1979 at Hacettepe Children's Hospital are presented.

Case Report

The four girls and two boys included in this study were between 3 and 14 months of age. Family history revealed that the parents of all these patients were first cousins.

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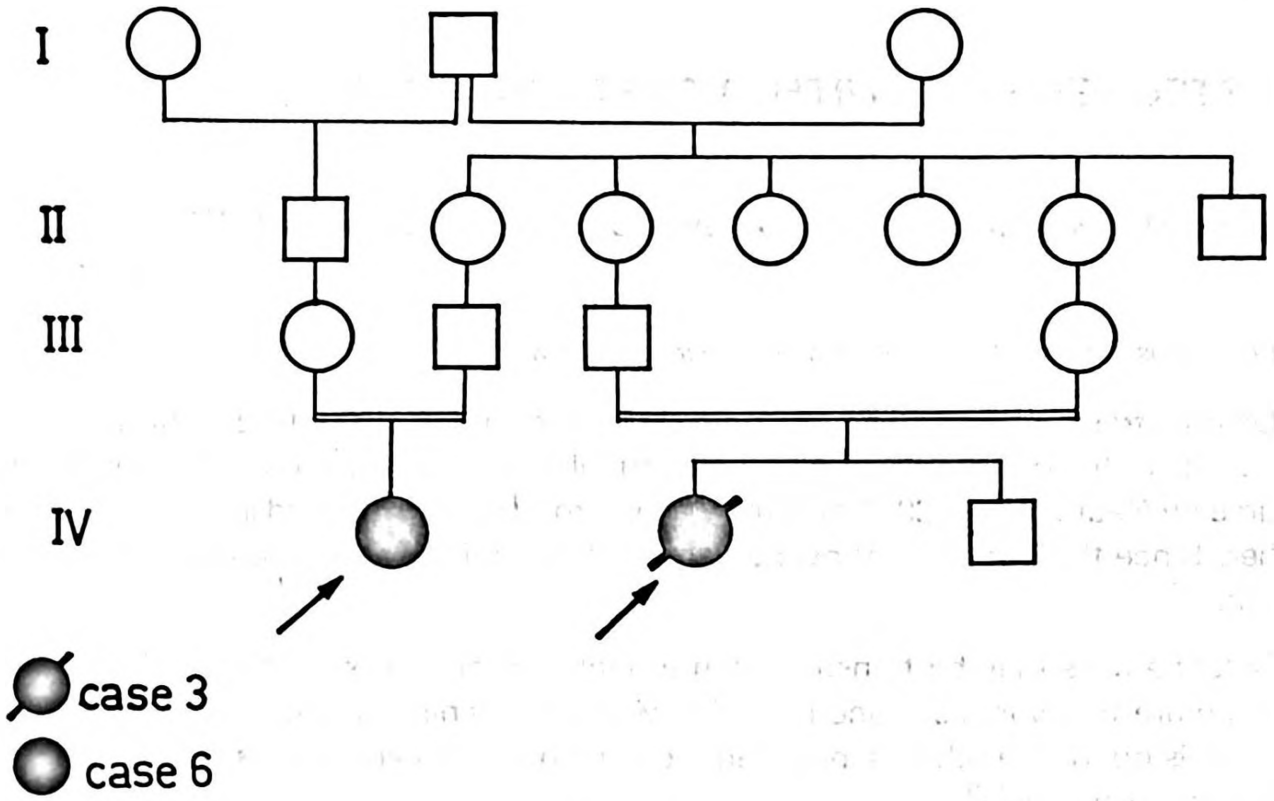


Figure 1

Pedigree of (cases 3 and 6) family

In addition, Case 3 and Case 6 were second cousins whose paternal grandmothers were siblings (Figure 1). No other cases of osteopetrosis were seen in these families. Pregnancy and delivery had been uneventful in all cases.

The manifestations of the disease in our patients are summarized in Table I.

All the patients were brought to the hospital with the chief complaints of failure to thrive, mental and motor retardation, fever and coughing. Physical examination revealed malnutrition and marked growth retardation in all cases. Hepatosplenomegaly, microcephaly, exophthalmos, sun-set sign, blue sclera, optic atrophy, nystagmus and anemia were also demonstrated in most of the cases. Other findings included marked signs of rickets: rachitic rosary and metaphyseal enlargement of both wrists.

Laboratory examination revealed hemoglobin levels between 3.10 and 14.40 gm/dl and WBC counts between 5,000 and 48,000 per mm^3. The peripheral smears showed obvious polychromatophilia. Repeated blood smears revealed in most of the cases the presence of occasional normoblasts and early myeloid elements such as myelocytes (Table II).

Blood chemistry examinations revealed calcium levels between 7.7 and 10.9 mg/dl and alkaline phosphatase from 8.9 to 30 Bodansky units (Table III). Urinalysis showed no abnormalities.

TABLE I

FINDINGS OF THE PATIENTS WITH OSTEOPETROSIS

Case no.	1	2	3	4	5	6
Age (mo.), sex	5 M	6 F	5 F	14 M	3 F	5 F
Growth failure	+	+	+	+	+	+
Microcephaly	+	+	—	+	+	+
Exophthalmos	+	+	+	+	+	+
Sun-set sign	—	+	+	—	—	+
Blue sclera	+	?	+	+	—	+
Optic atrophy	+	+	+	+	—	+
Nystagmus	—	+	+	+	—	+
Anemia	+	+	—	—	+	+
Hepatomegaly	4 cm	5 cm	6 cm	3 cm	3 cm	9 cm
Splenomegaly	4 cm	6 cm	9 cm	—	8 cm	6 cm
Others	Pes-equino varus	Seborrheic dermatitis			Seborrheic dermatitis spasticity	Hemangioma

TABLE II

LABORATORY FINDINGS OF THE PATIENTS WITH OSTEOPETROSIS

Case no.	Hb gm/dl	Hct	WBC $10^3/mm^3$	Reticulocytes	Peripheral blood smear: Young myeloid cell (%)	Peripheral blood smear: Nucleated RBC (%)	Platelets	Bone marrow
1	7.66	23	48.0	1.8	21	15	+	Hypocellular
2	3.10	—	25.5	3.4	4	17	+ + +	Hypocellular
3	7.20	25	7.0	—	14	7	+ +	Not performed
4	14.40	36	5.0	1.0	—	—	+ + +	Not performed
5	8.55	28	13.0	—	7	3	+	Hypocellular
6	8.31	25	13.6	2.6	6	—	+ + +	Hypocellular

(+) Few (+ + +) Normal

TABLE III

CALCIUM, PHOSPHORUS AND ALKALINE PHOSPHATASE VALUES OF THE PATIENTS WITH OSTEOPETROSIS

Case No.	Calcium mg/dl	Phosphorus mg/dl	Alkaline phosphatase Bodansky units (BU)
1	7.7	3.8	27.8
2	10.2	2.4	20.0
3	9.6	4.5	10.0
4	9.6	3.6	30.0
5	8.6	2.5	19.7
6	10.9	2.5	8.9

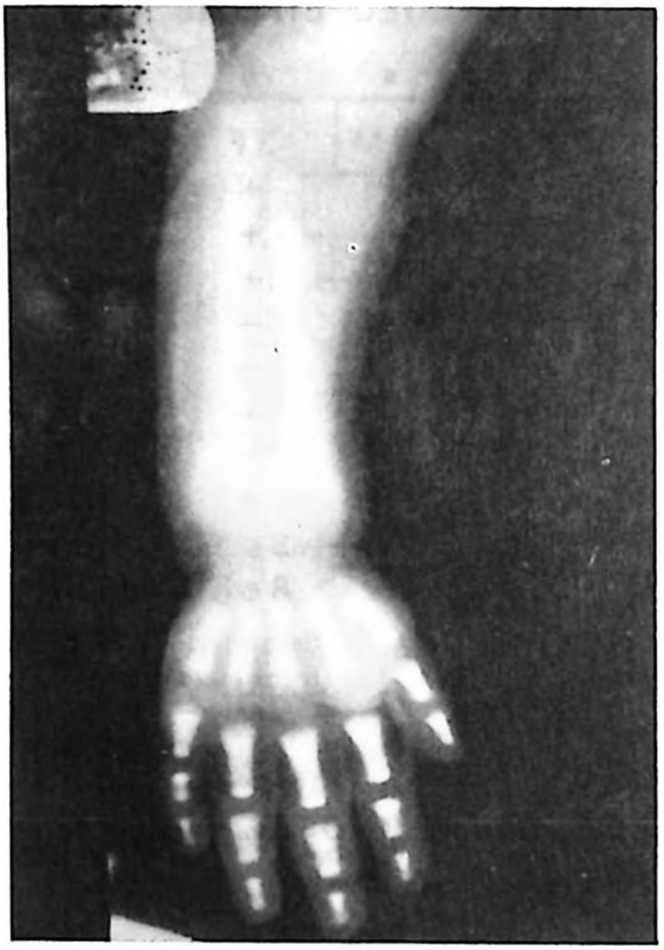


Figure 2

Radiogram of the extremities shows sclerosis. The metaphyses of the long bones reveal findings of rickets (Case 3).

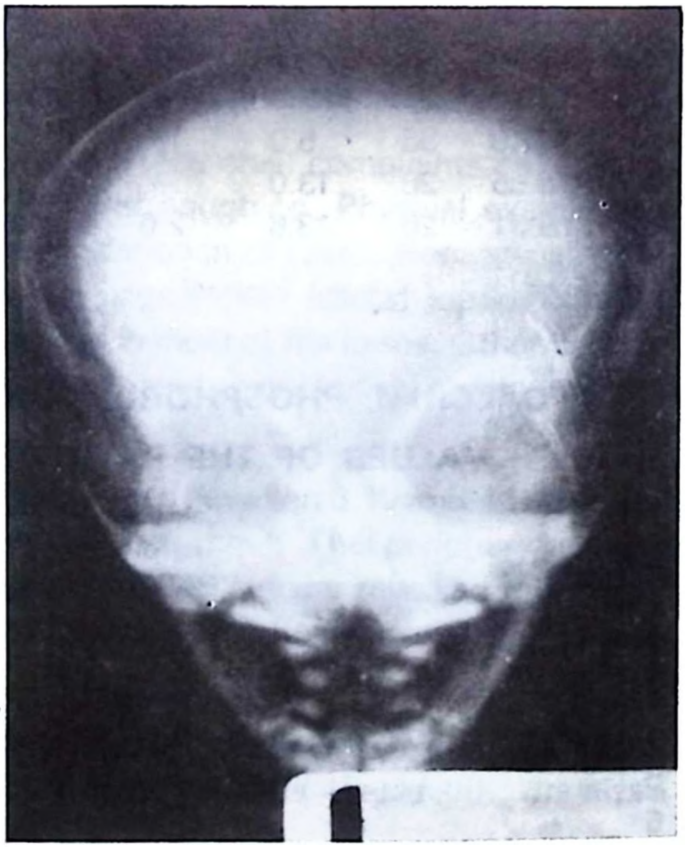
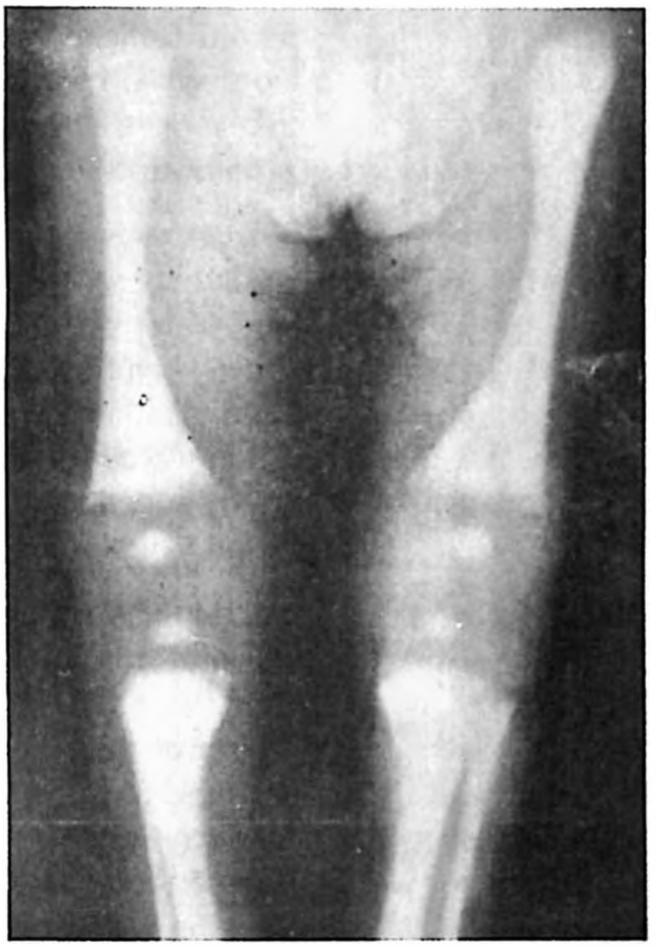


Figure 3

Radiograms of the skull reveal pronounced osteosclerosis at the base of the skull (Case 4).

Figure 4

Radiograms of the pelvis and lower extremities show the presence of generalized increase in bone density. This osteosclerosis is present notwithstanding marked findings of rickets in the metaphyses of the long bones (Case 5).



X-rays of the bones revealed generalized increased bone density in all patients. There was also flaring and irregular ossification of the metaphyses indicating the presence of active rickets (Figures 2-4).

Radioactive studies were performed in three patients. Total bone survey with Tc^{99m} pyrophosphate demonstrated normal activity in all patients. Reticuloendothelial system survey with Tc^{99m} colloid sulphur demonstrated suppression of bone marrow activity. Liver scan revealed nonspecific hepatosplenomegaly in two patients and normal activity in one who had neither anemia nor splenomegaly.

Discussion

In spite of a lack of cases published in the literature between 1930 and 1975[6,10-12], textbooks[2] do report a high incidence of rickets among children with osteopetrosis. Recently, in addition to two cases published in India[10], six patients out of 26 with osteopetrosis have been reported with rickets[1].

The cases of osteopetrosis associated with rickets are found either in the early literature or in the developing countries such as Turkey, where vitamin D deficiency

rickets is still fairly common. Deficiency in vitamin D causes impairment in epiphyseal calcium deposition, while metaphyseal thickening may continue due to osteopetrosis. Competition for the calcium may aggravate the rickets by further decreasing the epiphyseal calcium deposition.

In osteopetrosis the bone marrow is reduced in volume due to increased thickness and density of the cortex and spongiosa of the bones[2]. The sclerosis involves all skeletal tissue during the skeletal development. X-rays show marked generalized osteosclerosis, with rickets-like clubbing of the metaphyses of the long bones[14]. Hypocalcemia is seen in some patients and rickets-like changes suggest that there may be some disturbances in the calcium metabolism. But no primary disturbance of mineral metabolism or dysfunction of the parathyroid glands have been observed, and no disorder linked to vitamin D metabolism has been demonstrated[8,14].

Active rickets was established in all our cases through radiological studies. X-rays showed a generalized increase in bone density. Osteosclerosis was present with marked findings of rickets in the metaphyses of the long bones. These metaphyses revealed flaring and widening of the epiphyseal plate. The osseous trabeculation was very coarse in some cases. Skull x-rays of the patients revealed pronounced osteosclerosis at the base of the skull. The bones of the calvarium showed some increase in density and the vertebrae and ribs also involved. The chostochondral junctions showed flaring and the ribs were thickened. Both these findings are typical of active rickets, which also was demonstrated biochemically in most of the cases (Figures 2-4). The chemical determinations shown in Table III revealed that serum alkaline phosphatase concentrations were elevated in four patients. Serum calcium concentrations were mildly decreased in two cases.

Anemia is often present in osteopetrosis and its severity is not necessarily correlated with the sclerosis of the bones. It seems that the anemia is an associated symptom of osteopetrosis and not the result of the marrow replacement by bone[2]. The cellular changes of the peripheral blood of patients with osteopetrosis are frequently similar to those of patients with myelofibrosis. The cause of myelofibrosis in osteopetrosis is not well known[15]. The marrow cavity is often obliterated by an overgrowth of abnormal bone and the hematopoietic tissue is replaced by varying degrees of fibrosis. The myeloid metaplasia of the liver and spleen is secondary or compensatory to the loss of the marrow function. On the other hand, the enlargement of the liver and spleen is parallel to the degree of fibrosis. Ischemia of the marrow may be a factor in the development of the hematological picture. The anemia may vary from a hypochromic to a hyperchromic type. The red cells show anisocytosis and poikilocytosis [2,15,16].

The blood pictures of our patients are shown in Table II. Five patients out of 6 had anemia. The hemoglobin levels varied from 3.10 to 8.55 gm/dl. Only one patient

had hepatomegaly without splenomegaly and anemia. Radioactive studies showed normal activity in the total bone and reticuloendothelial system of this patient. These findings suggest that this case may have been the benign form of osteopetrosis. Normoblasts, polychromatophilia and immature myeloid elements in the smear of peripheral blood and hypocellular bone marrow suggested that the other 5 patients had myelofibrosis.

There is no effective treatment for osteopetrosis, rickets and myelofibrosis because the etiology of this condition is unknown[2]. Several investigators have suggested that corticosteroid therapy results in an increased hemoglobin concentration and platelet count with a decrease in the size of the spleen. Blood transfusions are also helpful for the anemia [1,2,14,17].

We used prednisolone 2 mg/kg/day in our last patient. The hemoglobin level was raised from 8.2 to 10.3 gm/dl and spleen size decreased by 2 cm in one month. This patient is still on prednisolone treatment. Due to lack of further experience, we cannot say whether the corticosteroid treatment is helpful or not.

Summary

Six cases (4 girls and 2 boys aged 3 to 14 months) with osteopetrosis associated with rickets are presented. The parents of all these patients were first cousins. In all patients, physical examination revealed malnutrition and marked growth retardation. Hepatosplenomegaly, microcephaly, exophthalmos, sun-set sign, blue sclera, optic atrophy, nystagmus and anemia were also demonstrated in most cases. Other findings included marked signs of rickets: rachitic rosary and metaphyseal enlargement of the wrists.

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