ORIGINAL PAPER

OSTEOPETROSIS IN CHILDREN

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SUMMARY Over a 10-year period, 28 Arab children with autosomal recessive osteopetrosis were seen in two hospitals in Riyadh, Saudi Arabia. Eighteen (64%) had osteopetrosis associated with metabolic acidosis probably due to a renal tubular defect; nine (32%) had a malignant infantile form of osteopetrosis and one had a mild form with delayed onset. Parental consanguinity was 56% and 40% among patients with and without acidosis respectively. Somatic and psychomotor retardation and recurrent bone fractures were common in both groups. Dental caries, cerebral calcification and optic atrophy were more frequent in patients with acidosis, while anaemia, hepatosplenomegaly and deafness were more common in patients without acidosis. To guarantee optimal rehabilitation, children with this progressive disease require an early multiteam approach. (*Int J Clin Pract* 1998; **52(1)**: 15-18)

Osteopetrosis was first described in 1904 by Albers-Schönberg.[1] It is a rare disorder characterised by increased bone density and abnormalities of bone remodelling due to impaired lysosomal function of osteoclasts and their precursor cells, monocytes.[2] The condition is broadly divided into two categories: benign autosomal dominant and autosomal recessive. The latter has been subdivided into three groups: a form associated with renal tubular acidosis (RTA), an infantile (malignant) form, and a mild form with dysmorphic features.[3]

Here, we report on our experiences with 28 patients from Saudi Arabia to delineate the prevalent types of this disorder in this country. Patients previously reported from the same institutions were excluded.[4,5]

MATERIALS AND METHODS

The case records of 28 patients with osteopetrosis, seen over a 10-year period (1984-1994) in two hospitals in Riyadh, were reviewed. The diagnosis was made on the basis of the classic radiological signs: increased bone density and expansion of the ends of the long bones (Figure 1). The case records were analysed according to age, sex, family history, presenting symptoms, physical signs, radiological manifestations and other ancillary investigations, mode of therapy and length of follow-up. Patients were divided into two groups according to the presence of metabolic acidosis (pH <7.35, HCO_3 <18 mmol/l) as documented by the results of two or three arterial blood gases. Parents and siblings of index cases were screened for radiological evidence of osteopetrosis.

RESULTS

All the patients were Saudi nationals of Arab origin from the Central and Northern provinces. Group A consisted of 18

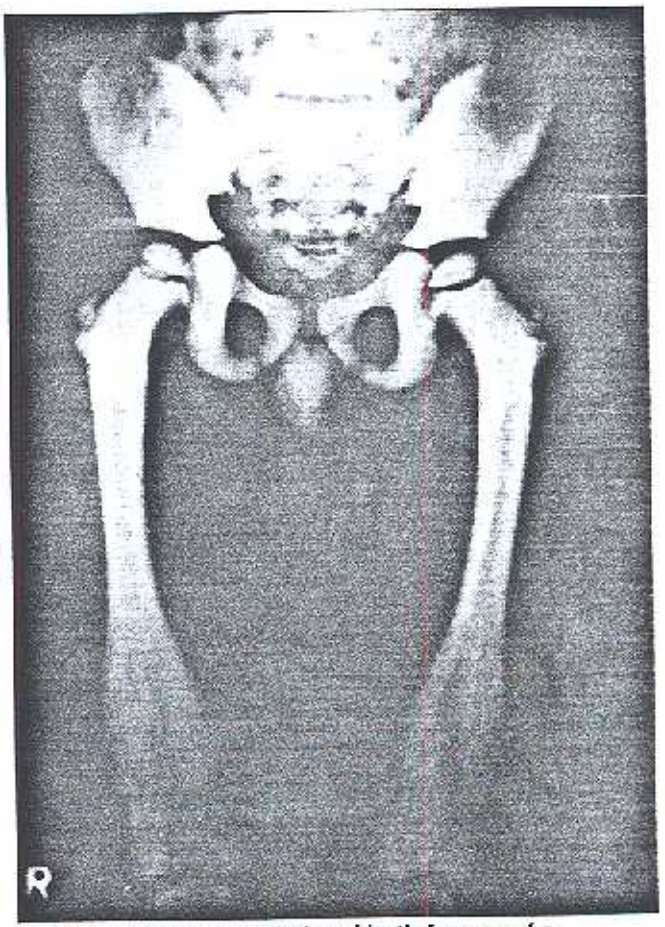

Figure 1. Roentgenography of both femora of a 7-year-old male with osteopetrosis showing generalised sclerosis of the bones, with metaphysis widening and cortical thickening

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Table 1. Clinical findings in 28 patients with osteopetrosis at time of presentation

	Group A With acidosis (n=18)	Group B Without acidosis (n=10)
Male/female	1:1	3:2
Age range (median)	2m-15y (3y 3m)	2-11m (6m)[1] + 14y[2]
Height <3rd centile	13 (72%)	7 (70%)
Weight <3rd centile	13 (72%)	7 (70%)
Dental caries	13 (72.2%)	4 (40%)
Hepatomegaly	3 (17%)	8 (80%)
Splenomegaly	3 (17%)	8 (80%)
Repeated fractures	7 (39%)	4 (40%)
Psychomotor retardation	10 (56%)	5 (50%)
Nystagmus	4 (22.2%)	2 (20%)
Squint	4 (22.2%)	2 (20%)
Deafness	0 (0%)	2 (20%)
Cerebral calcification by CT	3/10 (30%)	0/5 (0%)
Optic atrophy	5 (28%)	2 (20%)
Follow-up (mean)	1m-10y (46.2m)	1m-4y (17.8m)

[1] 9 patients with malignant osteopetrosis. [2] 1 patient with mild form; m: month; y: year

children from 10 families with osteopetrosis and metabolic acidosis. The male to female ratio was 1:1. Parental consanguinity was found in 10 patients in seven sibships (56%). Eight patients in six sibships came from first cousin marriages and in two patients (brothers) the parents were second cousins. In the other eight patients in six sibships, consanguinity could not be confirmed. Radiological screening of the parents' femora gave normal results.

There were 10 patients from 10 sibships with osteopetrosis without evidence of metabolic acidosis (group B). The male to female ratio was 3:2. Parental consanguinity was found in four (40%) patients. In the other six patients, consanguinity could not be confirmed, but two of them had a family history of a previous sibling or a cousin with osteopetrosis. All patients were diagnosed during the first year of life except one who presented at 14 years old with recurrent bone fractures, short stature, dental caries, psychomotor retardation and bilateral optic atrophy. She had mild anaemia but no hepatosplenomegaly or metabolic acidosis.

Tables 1 and 2 summarise the clinical and laboratory findings in the two groups. Growth retardation was evident in both groups. Formal psychomotor assessment was not feasible, but on clinical developmental assessment almost 50% of the patients in each group were severely retarded. Dental caries and cerebral calcification were more predominant in group A, whereas hepatosplenomegaly, anaemia and thrombocytopenia were predominant in group B. Haemoglobin below 100 g/l was found in three patients in group A and in five patients in group B. Thrombocytopenia (platelets <150 x 10^9/l) was found in four patients in group B only. Serum calcium, phosphate and alkaline phosphatase were normal, except in two patients in group B with mild hypocalcaemia and high alkaline phosphatase; both had concomitant rickets.

Table 3 summarises some of the pertinent laboratory finding in group A and confirms the finding of normal anion gap metabolic acidosis, which is the main feature of renal tubular acidosis. Using a freshly voided morning urine sample, seven patients demonstrated alkaline urine pH (pH1 >5.5)

Table 2. Laboratory findings in 28 patients with osteopetrosis at time of presentation

	Group A With acidosis (n=18)		Group B Without acidosis (n=10)	
	Range	Median	Range	Median
Hb (g/l)	75-147	107	52-119	92
WBC (10^9/l)	5.2-19.4	9.0	7.6-38.3	11.9
Platelets (10^9/l)	165-545	290	75-372	320
Ca (mmol/l)	1.9-2.7	2.4	1.8-2.6	2.3
PO_4 (mmol/l)	1.3-2.0	1.6	0.76-1.9	1.26
Alkaline phosphatase (UI)	86-392	198	135-1800	224
HCO_3 (mmol/l)	10-17	14	16-30	22

measured by a pH meter, and positive urinary anion gap [(Na+K)-CL]. One patient in group A (5.6%) and five in group B (50%) received blood transfusion. Eleven patients in group A were treated with large doses (>6 mmol/kg/day) of sodium bicarbonate for a relatively short period (six months to two years). In two patients treated for three-year period, the growth velocity was maintained but not accelerated. Seven patients in the same group required supplementation with potassium chloride. The rest received conservative medical therapy which consisted of nutritional support with a low calcium and high phosphate diet. Episodes of infection were treated with the appropriate antibiotics. Bone fractures were dealt with by the orthopaedic surgeon. Three patients in group B aged 3-4 years died of septicaemia.

DISCUSSION

Osteopetrosis is relatively frequent in Saudi Arabia. This series included the largest number of patients so far reported in this country.[1,9] Nearly 50 patients with osteopetrosis with renal tubular acidosis secondary to carbonic anhydrase II (CAII) deficiency have been mentioned in the medical literature; 25 of them were from Saudi Arabia.[10] The condition is also relatively common in the neighbouring country of Kuwait,[11] and has been attributed to the high rate of consanguinous marriages.[4,11] In this series, parental consanguinity was found in 56% and 40% of patients with osteopetrosis with and without acidosis respectively. This fact, together with lack of evidence of the disease in parents, favours an autosomal recessive inheritance.

Kahler *et al*[3] have suggested that the autosomal recessive category has three clinical patterns: the severe form of the disease with renal tubular acidosis;[4,9,12] the severe malignant form presenting in the first year of life with anaemia, hepatosplenomegaly and increased susceptibility to infection and death from sepsis and heart failure;[4,11,12] and the mild form which presents with anaemia, multiple fractures, dental caries and short stature without evidence of renal tubular acidosis.[3] In this series, 18 cases of the first pattern, nine of the second and one of the third were identified.

CAII deficiency can be diagnosed biochemically by demonstrating a severe selective reduction of CAII in erythrocyte lysates, as previously described.[13] Unfortunately this facility is not available locally. However, the presence of acidosis, the characteristic clinical presentation and the

Table 3. Laboratory findings in 18 patients with osteopetrosis and RTA (group A) at time of diagnosis

	Serum						Urine		
Case No	Creatinine (μmol/l)	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	TCO_2 (mmol/l)	pH	pH	AG	Density (kg/l)
1	34	137	3.3	112	16	7.23	6	–	1015
2	50	136	3.2	113	15	7.28	6.5	+	1010
3	43	140	3.0	114	11	7.20	5.3	–	1006
4	33	137	3.5	111	15	7.20	7	+	1015
5	63	141	4.4	116	16	7.3	6	+	1015
6	42	133	3.8	113	12	7.25	7	+	1009
7	45	138	5.5	114	10	7.32	5	–	1010
8	36	138	3.4	113	16	7.3	7.5	+	1014
9	30	139	3.4	114	15	7.26	6	+	1030
10	48	139	3.6	111	17	7.28	6	+	1020
11	20	129	4.1	112	11	7.20	7	NA	1018
12	45	141	4.1	115	13	7.27	7.5	NA	1010
13	35	142	4.2	116	15	7.30	6	NA	1008
14	32	135	3.7	111	14	7.30	6.5	NA	1020
15	24	140	3.3	118	14	7.25	6.3	NA	1018
16	27	137	4.4	117	11	7.24	6.8	NA	1010
17	41	139	3.9	112	17	7.30	6.5	NA	1016
18	45	136	3.9	113	13	7.25	6	NA	1025

AG anion gap; NA not available

known high incidence of previously documented cases of this category from Saudi Arabia suggest that patients (group A) in our series belong to this category. In these patients, intrauterine growth is normal,[8] labour and delivery are usually uneventful and the condition is typically not recognised until late infancy or early childhood with developmental delay, failure to thrive, fractures and dental caries,[9,10] all of which are the main features in our patients (Table 1). The youngest child was a boy who was screened radiologically at 2 months old because of a previously affected sibling. His mother reported decreased fetal movement during pregnancy compared with her previous pregnancies. More than half of all patients suffer symptoms of cranial nerve compression.[11] Visual loss may result from pressure on the second cranial nerve[3] or without narrowing of the optic foramen.[9] Mental subnormality, of variable severity, is present in more than 90% of patients.[5,7] Ten (56%) patients in our group had profound psychomotor retardation. Severe mental retardation had previously been noted in patients with CAII deficiency from Saudi Arabia.[8] The skeletal changes resemble those of other forms of osteopetrosis[3] with two exceptions: the osteosclerosis and defective bone modelling can diminish spontaneously over decades and there is cerebral calcification.[9,10] Calcification in the basal ganglia region was evident in three patients (the CT was performed at 6-9 years of age). In the remaining seven patients the CT was performed at an earlier age (3-28 months) without evidence of calcification, supporting the previous observation that calcification appears at approximately 2-5 years of age and becomes more pronounced during childhood,[9] which emphasises the need to repeat the study at a later date. Intracranial calcification has been reported in association with a lethal autosomal recessive syndrome that mimics CAII deficiency and is characterised by generalised osteosclerosis, cerebral calcification, craniofacial dysostosis, microthorax, and absence of RTA.[5,10] None of the patients in group A had these characteristics.

The presence of hyperchloraemic acidosis with a normal serum anion gap in group A is suggestive of RTA (Table 3). Either proximal or distal RTA, or both together, have been reported.[10] In our series, seven patients had alkaline urine pH and a positive urinary anion gap, which strongly suggests distal RTA.[20] Further studies to differentiate the type of acidosis could not be performed in our patients.

Long-term bicarbonate treatment has been tried in a few subjects, with either an accelerating or a negative effect on growth velocity.[9,12]

Malignant infantile autosomal recessive osteopetrosis was diagnosed in 9 out of 10 patients in group B, based on the characteristic early presentation in the first year of life, the associated haematological findings and the absence of acidosis as shown in Tables 1 and 2. Recurrent infection and septicaemia were the main causes of death in this group.[4,11,13] Growth retardation and hepatosplenomegaly as a consequence of extramedullary erythropoiesis is a frequent finding (80%). The incidence of hepatosplenomegaly in previous reports ranged from 30 to 100%.[4,11,13] Anaemia was common, as reported by others.[11] Dental caries was seen in 40% of our patients, compared with 100% in other reports.[14] This was because most of our patients were very young and in only a few had their teeth erupted.

The treatment of this group of patients was mainly supportive. Other options that have been tried with some success include prednisolone,[23] high dose calcitriol[24] and bone marrow transplantation,[25] but none of these was tried in our patients. Bone densitometry may be of prognostic value in follow-up, especially in monitoring the response to such therapy.[26]

CONCLUSION

We have presented the clinical chasteristics of three different forms of autosomal recessive osteopetrosis as observed in Saudi Arabia. The diagnosis is based on a positive family

history with parental consanguinity and typical radiological findings. Osteopetrosis associated with RTA differs from the malignant infantile form by a higher incidence of dental caries and cerebral calcifications and a lower frequency of anaemia and hepatosplenomegaly. Osteopetrosis frequently leads to multiple handicaps and requires an early aggressive multiteam approach to improve rehabilitation.

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