Osteopetrosis

J. S. YU,* R. K. OATES, K. HELEN WALSH, and SUSAN J. STUCKEY

From the Department of Child Health, University of Sydney, and Department of Dietetics, Royal Alexandra Hospital for Children, Camperdown, N.S.W., Australia

Yu, J. S., Oates, R. K., Walsh, K. H., and Stuckey, S. J. (1971). *Archives of Disease in Childhood*, 46, 257. **Osteopetrosis.** The clinical histories of nine children with osteopetrosis are reported. Two of them had the malignant infantile variety of the disease: one died within 3 months of birth and the other has survived 20 months on a regimen of a low calcium intake, cellulose phosphate, and steroids. The beneficial effect of a low calcium intake, in early infancy, is supported by the clinical course in the infant with the malignant variety and in another child with the more benign form of the disease. No calcium balance studies were performed.

This study suggests that the active measures outlined may favourably influence the haematological and osteosclerotic course of the disease, pending further knowledge of its aetiological basis, and more specific therapy.

Osteopetrosis or marble bone disease is a rare metabolic bone disease characterized by dense bones (Albers-Schönberg, 1904; Karshner, 1926). Two varieties have been clearly defined—an infantile progressive disease and a milder benign disease of later childhood and adolescence (Turano, Fagan, and Corbo, 1954; Enell and Pehrson, 1958). The two forms appear differently both clinically and genetically. A dominant pattern of inheritance is usually seen in the benign type while the severe infantile type is usually inherited as a Mendelian recessive.

In the progressive infantile variety, the infants rarely survive the first year of life and often suffer from nerve pressure effects when the foramina in the skull fail to enlarge during growth. Blindness and deafness may result. Some of these infants develop hepatosplenomegaly and anaemia and pursue a rapid downhill course. The anaemia is generally haemolytic and, with thrombocytopenia, seems to be related to hypersplenism (Engfeldt, Karlberg, and Zetterström, 1955; Gamsu, Lorber, and Rendle-Short, 1961; Sjölin, 1959). Good responses have been reported with splenectomy (Besselman, 1966) and with corticosteroids (Moe and Skjaeveland, 1969).

The increased bone density and the accompanying increase in positive calcium balance (Dent, Smellie, and Watson, 1965) is a more difficult problem. It has been difficult to achieve a less

positive calcium balance with a diet low in calcium and with steroids (Morrow *et al.*, 1967). This approach to management has been recently criticized by Cohen (Children's Hospital Medical Center, Boston, 1965). We report here our experiences in two infants whose calcium intake was restricted. The clinical features in 7 other cases are also described.

The clinical histories of 9 children with osteopetrosis seen at the Royal Alexandra Hospital for Children from January 1950 to January 1970 are recorded (Table), the case histories of the last 3 infants being described in greater detail. Two of them had the malignant variety of the disease, one died at 3 months and the other has survived 20 months on a regimen of corticosteroids and dietary restriction of calcium. The third case was submitted to a dietary restriction of calcium for 10 months in early infancy and then allowed to revert to a normal diet when her bone density became less on radiological examination. After 4 years of good health she developed bone symptoms.

This remission and relapse appear to be unique and may lend support to the arguments that dietary calcium restrictions do influence the natural history of the disease.

Case Records

Case 1. This child was born 10 days past term to unrelated Portuguese parents. The pregnancy and delivery were normal. His birthweight was 3500 g. At the age of 1 month he had an umbilical hernia

TABLE
Clinical Summary of Cases

Case No.	Date of Birth and Sex	Age at Diagnosis	Presenting Symptoms or Signs	Radiological Changes in Bones	Haematological Involvement	Nerve Pressure	Family History	Outcome and Comment
1	4.10.68 Female	7 mth	Anaemia; respiratory infections	Increased density	Haemolytic anaemia	Nil	Nil	Malignant recessive variety; progressing well on prednisone and low calcium diet
2	24.7.69 Female	2 mth	Failure to thrive	Increased density	Anaemia	Nil	Nil	Fever of unknown origin; died 4 weeks after admission; malignant recessive variety
3	23.3.65 Female	3 wk	Neonatal respiratory distress	Increased density	Nil	Nil	Nil	Low calcium diet from 1 to 11 mth; pathological fracture at 4½ yr; probably benign dominant variety
4	8.12.60 Female	4 mth	Birth asphyxia; cerebral palsy	Increased density; bone within bone appearance	Nil	Nil	Adopted baby	Recurrent fractures and spastic; probably benign dominant variety
5	8.12.61 Male	5 mth	Oxycephaly and cranio-stenosis	Increased density; bone within bone appearance, lack of modelling	Nil	Bilateral optic atrophy	Nil	Craniectomy; arachnoid cyst; died with pneumonia; no necropsy; probably dominant variety
6	1.2.66 Female	12 mth	Pneumonia; cerebral palsy	Increased density	Nil	Nil	None obtained	Died from infection; no necropsy; probably benign dominant variety
7	23.7.51 Female	3 yr, 9 mth	Nil; family survey	Increased density; bone within bone; sandwich vertebrae	Nil	Nil	Yes	Well, benign dominant variety
8	26.6.55 Female	11 yr	Bony pain	Increased density; bone within bone; sandwich vertebrae	Nil	Nil	Yes	Benign dominant variety
9	25.4.54 Female	12 mth	Blindness	Increased density; small optic foramina	Nil	Bilateral optic atrophy	Yes	Blind and retarded; severe expression of dominant variety

repaired and from this age suffered from a persistent cough and frequent upper respiratory tract infections. He had never been a very active baby. His parents sought advice about his persistent cough at 7 months. Pallor was noticed and he was referred for investigation of anaemia.

On examination he was pale, his head circumference was 47 cm (above the 90th centile) and his weight was 6.5 kg (below the 10th centile). The anterior fontanelle was widely open but flat and the fundi were normal. He was unable to sit without support and would not bear weight on his legs. His hands were short but his general body proportions were normal. His liver was palpable 2 cm below the costal margin and his spleen was firm and enlarged 6 cm below the costal margin. A large periumbilical hernia was present adjacent to a herniorrhaphy scar. There were no other abnormal findings.

His haemoglobin was 8.6 g/100 ml, with a leuco-erythroblastic picture. Platelets were numerous and the white cell count was 7000/mm³, with 25% neutrophils, 57% lymphocytes, 4% eosinophils, 7% monocytes, and 7% primitive forms. Direct Coombs test was negative and there were no inclusion bodies in the red cells. The fetal haemoglobin was 2% and haemoglobin electrophoresis was normal. The serum calcium was 10 mg/100 ml, serum phosphorus 5 mg/100 ml, serum alkaline phosphatase 13 King-Armstrong units/100 ml, serum acid phosphatase 6 King-Armstrong units/100 ml, and serum magnesium 1.8 mEq/EEG.

A skeletal survey showed all the bones to be extremely dense with poor differentiation between cortex and medulla. Radiological studies on his sibs and parents were normal except for some increased density of the lower ends of his father's radius and ulna. Serum calcium, phosphorus, magnesium, alkaline phosphatase, and acid

phosphatase estimations were normal in the parents and the sib. There was no family history of bone diseases. A diagnosis of the malignant recessive form of osteopetrosis was made and a low calcium diet was started. A diet containing 50 mg calcium per day was given using a low calcium milk ('Locasol', Trufoods Ltd.), made with distilled water, low calcium solids, cellulose phosphate 10 g/day, and a multivitamin preparation without vitamin D. The diet provided 2.5 g protein/kg per day and 980 calories. The infant was seen initially every 2 weeks and then monthly. After 5 months on this regimen, his bones were unchanged in density, the blood chemistry remained normal with no significant change in calcium, phosphorus, or alkaline phosphatase, but his spleen was slowly enlarging and his haemoglobin remained low at 8.9 g/100 ml. The reticulocyte count slowly climbed to 13%. Because of this continuing haemolysis prednisone 10 mg daily was started. 4 weeks later the haemoglobin had risen to 11.4 g/100 ml and his spleen began to decrease in size. The improvement in the blood picture continued and the spleen became just palpable. With growth increments his calcium allowance was increased to 90 mg/day and his protein intake increased.

After 3 months the prednisone was decreased to 7.5 mg daily without any alteration in his clinical response. His progress is shown in Fig. 1.

FIG. 1.—Clinical course in Case 1.

Case 2. This child was born at 34 weeks' gestation after a normal labour and delivery. Her birthweight was 2.5 kg.

After birth she gained weight poorly, was difficult to feed, and was noted to be pale and listless. She was admitted to hospital at 2 months of age for investigation

of failure to thrive. On examination her weight was 3.02 kg and her head circumference 36 cm (both below 10th centile). She was pale and there was mild frontal bossing. The liver edge was palpable 3 cm below the right costal margin and the spleen was just palpable. A skeletal survey showed increased density of all bones and fractures in each humerus, each femur, and the left clavicle. The metaphyses of the limbs were irregular and suggestive of rickets. The haemoglobin was 7.5 g/100 ml, white cell count was 12,000/mm³, with a normal distribution but the neutrophils showing a shift to the left. Serum calcium was 9.5 mg/100 ml, phosphorus 2.6 mg/100 ml, and serum alkaline phosphatase 100 King-Armstrong units/100 ml. A diagnosis of osteopetrosis was made.

She remained difficult to feed while in hospital and gained very little weight. Vitamin D (10,000 IU daily) was started 12 days after admission, but there was little apparent improvement. She developed an intermittent fever, continued to deteriorate, and died 4 weeks after admission.

Necropsy showed widespread reduction of marrow which was replaced by confluent rounded islands of acellular hyaline cartilage, surrounded by crescents of osteoid. The cartilaginous and bony portions were heavily calcified. Osteoclasts were very plentiful in some areas and decreased in others. There were also features consistent with secondary rickets. The liver and spleen were enlarged and showed extramedullary haemopoiesis. The diagnosis of osteopetrosis was confirmed.

Case 3. Born by elective caesarian section because of a breech presentation and disproportion. The mother had taken amylobarbitone and fluoride tablets for the first 6 months of pregnancy, and iron supplements and a diuretic during the last trimester.

The birthweight was 3.4 kg. There was some asphyxia at birth with an Apgar rating of 4 at 1 minute and 8 at 5 minutes. Because she became cyanosed on crying, a chest x-ray was taken at 18 days. The heart and lung fields appeared normal, but the ribs and vertebrae were abnormally dense. A skeletal survey showed uniform increase in the density of all bones. The appearance was consistent with a diagnosis of osteopetrosis (Fig. 2). The haemoglobin was 23.3 g/100 ml. Neither parent had any x-ray evidence of osteopetrosis nor had any relative suffered from generalized bone disease.

At 1 month of age Hb was 20.1 g/100 ml and the blood film normal. She was continued on breast feeding but a low calcium milk (Locasol, Trufoods Ltd.) was given as a supplement. A further skeletal survey at 2 months showed no change. By 3 months of age, she had been completely weaned on to 'Locasol', now made with distilled water. A multivitamin preparation without vitamin D was added and rice cereal was permitted. Serum calcium 9.7 mg/100 ml, serum phosphorus 6.8 mg/100 ml, serum alkaline phosphatase 38 King-Armstrong units/100 ml. Hb 11.6 g/100 ml with a normal blood film.

FIG. 2.—X-rays of Case 3 showing hand and wrist, and lower limbs. (a) At 3 weeks before treatment showing dense bones and the lack of moulding. (b) At 6 months showing decreased density following treatment. (c) At 5 years showing the return of bone density and pathological fracture at neck of right femur (see opposite).

Her milestones were normal when seen at 5 months. Her haemoglobin and blood chemistry remained unchanged. X-rays of the wrists and knees showed that the increased density was now not as marked and doubts were raised about the diagnosis of osteopetrosis. She was continued on her low calcium diet.

At 7 months she was allowed fruits, vegetables, rice cereal, and her 'Locasol' was now made with tap water. The serum calcium, phosphorus, alkaline phosphatase, and Hb showed no significant change. At 11 months the 'Locasol' was suspended and cow's milk in limited quantities introduced into her diet. An otherwise

FIG. 2c.—For legend, see opposite.

normal diet was given. X-rays of the long bones still showed some increased density in the metaphyseal regions.

She remained well and at 2½ years the only clinical abnormality was the rather dolichocephalic shape of her skull. Her head circumference was just above the 90th centile for her age.

At 3 years, further x-rays again revealed heavy mineralization of the bones of the skull and limbs. The metaphyseal areas were particularly affected and the diagnosis of osteopetrosis now seemed undeniable.

At 4½ years the patient developed a painful hip after a febrile illness. She was treated for a pathological fracture of the neck of the right femur with superimposed low-grade osteomyelitis. By 5½ years she had made a good recovery and seemed otherwise well. Her height was on the 10th centile and weight near the 50th centile for her age. Her head was dolichocephalic with frontal bossing. X-rays did not show any change in bone density. Hb 15.1 g/100 ml and blood film normal.

Comments

The mode of inheritance of osteopetrosis has appeared confused for many years. A hereditary pattern was first recognized in the differing degrees of clinical severity by Allan (1939). The complex nature of the inheritance is seen in the classification of Schinz (1944) and Hanhart (1948). The genetic problems were well reviewed recently by Johnston *et al.* (1968). Johnston *et al.* described

two modes of inheritance, a dominant form with a rather benign course and a more rare recessive form which runs a malignant course with marked anaemia, myeloid metaplasia, infection, and frequent early death. In the dominant variety, expressivity varies considerably within a family, ranging from an isolated radiological abnormality to fractures and cranial nerve involvement due to bone pressure at the skull foramina.

Of the 9 children admitted to this hospital over a 20-year period, 2 infants had the recessive variety while the other 7 had the clinical pattern of the dominant type, but family histories were not always present or available in these 7 children. Because of the benign nature of the condition in many patients with the dominant variety, the relative frequency of the 2 types in our community cannot be assessed on these figures.

In those children with the dominant type the severity of the disease was very variable. Some infants did indeed merit the label benign dominant, while in others the condition was far from benign, the children being severely disabled by fractures and cranial nerve lesions.

The management of the osseous anomaly has been either symptomatic, directed at the complications, or based on attempts to influence bone calcification or reabsorption. Cranial nerve pressure at the sites at which the nerve emerges from the skull

is a common problem, the most worrying being optic nerve atrophy. Successful orbital decompression has been reported (Hill and Charlton, 1965; Moe and Skjaeveland, 1969) while the usual orthopaedic principles have been applied to fractures which heal in the normal manner.

The underlying metabolic defect in osteopetrosis is not known. Fairbank (1948) noted signs of fluctuating activity of the osteosclerotic process with the club-shaped metaphyses showing alternating transverse bands of varying density. In 1957, Dent suggested that this evidence pointed to a significant environmental influence on a 'presumed constant genetic biochemical abnormality'; and used this concept to develop his hypothesis that 'profound changes in the development of the disease process should follow regimes aimed to produce calcium depletion'. In 1965 he reported the successful management of an infant on a regimen producing a negative calcium balance (Dent *et al.*, 1965). Other workers have attempted to achieve a negative calcium balance by using heparin, parathyroid hormone, vitamin A, vitamin D, chelating agents, and corticosteroids (Morrow *et al.*, 1967; Moe and Skjaeveland, 1969). In none of these studies has the bone density, already apparent at the beginning of treatment, been influenced by attempts to achieve negative calcium balance. In Case 1 there has been no significant change in the radiological bone density despite good clinical improvement. His head circumference centiles have not altered though his height centiles have fallen. This fall, however, may be related to steroid treatment rather than to progressive bony involvement with the osteopetrotic process. No attempts were made to measure calcium balances in this or the other infants. The effects of therapy directed at calcium mobilization are more interesting though more speculative in Case 3. Bone films were taken on many occasions in the first two months of life and showed increased bone density (Fig. 2a). After 3 months on a low calcium diet the bone density was less (Fig. 2b). After 10 months the low calcium diet was abandoned, and by 4½ years her bone density had again increased considerably and she suffered a fractured neck of the femur. The present appearance of her bones (hand and wrist) is shown in Fig. 2c. Remissions and relapses in overall bone density have not been described to occur spontaneously in osteopetrosis, and it seems likely that this unusual clinical course was due to the regimen of low calcium intake early in life. Dent *et al.* (1965) reported that during vigorous dietary calcium depletion, dense bands did not appear in the bones of their patient and that there

was no apparent decrease in the density of the bones already formed.

These cases of osteopetrosis must not be confused with the transient osteosclerosis of the newborn (Caffey, 1961) where the increased bone density resolves spontaneously in the first 1 to 2 months of life and where there is no evidence of bone-marrow involvement. In our experience this phenomenon is more common in infants of diabetic mothers. Of the last 4 infants we have seen with neonatal osteosclerosis, 3 were born of diabetic mothers and all 3 infants suffered some of the known complications of the respiratory distress syndrome, hypoglycaemia, and persistent jaundice.

There is no doubt that the haematological state of Case 1 was favourably influenced by a small dose of prednisone. His haemoglobin rose, the reticulocyte count fell, and his large spleen decreased dramatically in size. Anaemia in infants with the malignant recessive type of osteopetrosis does not seem to be due to a failure of adequate erythropoiesis but rather to an extra corpuscular haemolytic process (Sjölin, 1959). Hypersplenism has been incriminated by many workers (Engfeldt *et al.*, 1955; Moe and Skjaeveland, 1969; Dent *et al.*, 1965). This evidence is supported by the good effects of splenectomy on the haemolytic anaemia (Besselman, 1966; Dent *et al.*, 1965). It is not clear why corticosteroids should influence a haemolytic anaemia which appears to be largely due to hypersplenism, but the experiences of Moe and Skjaeveland (1969) are as encouraging as that reported here.

Until the basic pathology of osteopetrosis is elucidated symptomatic treatment with steroids will help the anaemia and may allow splenectomy to be avoided, while treatment aimed at minimizing calcium absorption may prove to be beneficial in influencing the course of the bony abnormality.

Dr. W. Grigor kindly provided the clinical notes of Case 2 and Dr. J. R. Davis those of Case 4.

REFERENCES

- Albers-Schönberg, H. (1904). Röntgenbilder einer seltenen Knochenerkrankung. *Münchener Medizinische Wochenschrift*, **51**, 365.
- Allan, W. (1939). Relationship of hereditary pattern to clinical severity as illustrated by peroneal atrophy. *Archives of Internal Medicine*, **63**, 1123.
- Besselman, D. M. (1966). Splenectomy in the management of the anemia and thrombocytopenia of osteopetrosis. *Journal of Pediatrics*, **69**, 455.
- Caffey, J. (1961). *Pediatric X-ray Diagnosis*, p. 838. Year Book Medical Publications, Chicago.
- Children's Hospital Medical Center, Boston (1965). Clinical Pathological Conference. *Journal of Pediatrics*, **67**, 133.
- Dent, C. E. (1957). Forward to Symposium on inborn errors of metabolism. *American Journal of Medicine*, **22**, 671.
- Dent, C. E., Smellie, J. M., and Watson, L. (1965). Studies in osteopetrosis. *Archives of Disease in Childhood*, **40**, 7.

- Enell, H., and Pehrson, M. (1958). Studies on osteopetrosis. I. Clinical report of 3 cases with genetic considerations. *Acta Paediatrica Scandinavica*, **47**, 279.
- Engfeldt, B., Karlberg, P., and Zetterström, R. (1955). Studies on the skeletal changes and on the etiology of the anaemia in osteopetrosis. *Acta Pathologica et Microbiologica Scandinavica*, **36**, 10.
- Fairbank, H. A. T. (1948). Osteopetrosis: osteopetrosis generalisata, marble bones, Albers-Schönberg's disease, osteosclerosis fragilitas generalisata. *Journal of Bone and Joint Surgery*, **30B**, 339.
- Gamsu, H., Lorber, J., and Rendle-Short, J. (1961). Haemolytic anaemia on osteopetrosis. *Archives of Diseases in Childhood*, **36**, 494.
- Hanhart, E. (1948). Über die Genetik der einfach-rezessiven Formen der Marmorknochenkrankheit und zwei entsprechende Stammbäume aus der Schweiz. *Helvetica Paediatrica Acta*, **3**, 113.
- Hill, B. G., and Charlton, W. S. (1965). Albers-Schönberg disease. *Medical Journal of Australia*, **2**, 365.
- Johnston, C. C., Jr., Lavy, N., Lord, T., Vellios, F., Merritt, A. D., and Deiss, W. P., Jr. (1968). Osteopetrosis. *Medicine*, **47**, 146.
- Karshner, R. G. (1926). Osteopetrosis. *American Journal of Roentgenology*, **16**, 405.
- Moe, P. J., and Skjaeveland, A. (1969). Therapeutic studies in osteopetrosis. Report of 4 cases. *Acta Paediatrica*, **58**, 593.
- Morrow, G., III, Barnes, L. A., Fost, A., and Rasmussen, H. (1967). Calcium mobilisation in osteopetrosis. *American Journal of Diseases of Children*, **114**, 161.
- Schinz, H. R. (1944). Erbtypen und Formen bei Marmorknochenkrankung. *Der Erbarzt*, **12**, 33.
- Sjölin, S. (1959). Studies on osteopetrosis. II. Investigations concerning the nature of the anaemia. *Acta Paediatrica*, **48**, 529.
- Turano, A. F., Fagan, K. A., and Corbo, P. A. (1954). Variations in clinical manifestations of osteopetrosis: report of two cases. *Journal of Pediatrics*, **44**, 688.

Correspondence to Dr. J. S. Yu, Department of Child Health, Royal Alexandra Hospital for Children, Camperdown, N.S.W., Australia 2050.