Osteopetrosis

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

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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.
A herniorrhaphy was performed and from this age suffered from a persistent cough. His haemoglobin was 8.6 g/100 ml with a leucocyte count of 7,000/mm³. Plaques were numerous and painful. The white cell count was 7,000/mm³. His hands were swollen. The child was pale and had a very active baby. He had no other abnormal findings.

The clinical summary of the cases is as follows:

<table>
<thead>
<tr>
<th>Case</th>
<th>Date of Birth</th>
<th>Sex</th>
<th>Age</th>
<th>Symptom</th>
<th>Diagnosis</th>
<th>Radiological Features</th>
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<tbody>
<tr>
<td>1</td>
<td>4.10.68</td>
<td>Female</td>
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Phenotypic appearance and bone density were noted in the following cases:

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- Case 2: Normal
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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.

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 vertebral 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.
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
normal diet was given. X-rays of the long bones still showed some increased density in the metaphysial 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 metaphysial 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 reticuloocyte 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 largedue 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

Allan, W. (1939). Relationship of hereditary pattern to clinical severity as illustrated by peroneal atrophy. Archives of Internal Medicine, 63, 1123.
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