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Osteopetrosis : Report of two cases

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Abstract **Background** : Osteopetrosis is a rare congenital disorder in which the bones are overly dense due to failure in osteoclastic bone resorption. Symptoms can include fractures, frequent infections, blindness, deafness, and hydrocephalus.

Purpose : We report two cases of osteopetrosis. The first case is of a 4 year old girl with osteopetrosis and osteomyelitis in the left mandible. She also presented anemia, proptosis, and nystagmus. The osteomyelitis was treated with antibiotics(ceftriaxone). The second case is of a 4 year 5 month old girl, with osteopetrosis and multiple fractures, included both femora, left tibia, costae and clavicle. She also presented hydrocephalus, blindness due to bilateral optic atrophy, hearing impairment in the left side and obstructive sleep apnea syndrome(OSAS). The fractures were treated with closed reduction and a hip spica cast for the femur and long leg plaster for the tibia fracture. She received a ventriculo peritoneal shunt for the hydrocephalus.

Results : The osteomyelitis in the first patient was overcome, but could relapse. The fractures as well as hydrocephalus in the second case were also overcome, but many complications remain.

Conclusions : Patients with osteopetrosis suffer from many complications. Therefore, treatment should be based on a multidisciplinary approach. Osteomyelitis sometimes occurs in osteopetrosis. The mandible is a region commonly affected related with changes in growing teeth. The fragile bones in osteopetrosis are very susceptible to be fractured.

Introduction

Osteopetrosis is a rare congenital disorder in which the bones are overly dense, caused by an imbalance between the formation of bone and the breakdown of the bone. There are several types of osteopetrosis of various severities. Symptoms can include fractures, frequent infections, blindness, deafness, strokes and hydrocephalus.[1)–6)] Osteopetrosis is also known as Albers-Schonberg Disease, Generalized Congenital Osteosclerosis, Ivory Bones, Marble Bones, and Osteosclerosis Fragilis Generalisata.[5)]

The primary underlying defect in all types of osteopetrosis is failure of the osteoclast to reabsorb bone. This results in thickened sclerotic bones, which have poor mechanical prop-

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erties. Increased bone fragility results from a failure of the collagen fibers to connect osteons properly and from defective remodeling of woven bone to compact bone.[1) 3)]

A number of heterogeneous molecular or genetic defects can result in impaired osteoclastic function. The exact molecular defects or sites of these mutations have remained largely unknown. The defect might lie in the osteoclast lineage itself or in the mesenchymal cells that form and maintain the microenvironment required for proper osteoclast function.[1) 3)]

Many patients have bone pains. Bony defects are common and include cranial nerve entrapment neuropathies, carpal tunnel syndrome, and osteoarthritis. Bones are fragile and might fracture easily. Approximately 40% of patients have recurrent fractures. Osteomyelitis in the mandible occurs in 10% of patients. Extramedullary hematopoiesis might occur with resultant hepatosplenomegaly, hypersplenism, and hemolysis. Other manifestations include sleep apnea and blindness.[1) 6)]

Cases Report

The first case is of a 4-year-old girl, who came to the hospital with lump on the left mandible. The delivery was spontaneous. The patient was the first child of her parents. For the 4 months prior to admission she complained about the lump on her left mandible which grew very fast. The patient received several antibiotics from a general practitioner and a paeditrician with no improvement. At 2 weeks later, blood and pus came out from the lump. The patient was admitted to another hospital and received packed red cells and thrombocyte transfusion. But the anemia and thrombocytopenia recurred and she received repeated transfusions. Since about 5 months old, she has grown very slowly. She was anemic, with a lump on her left mandible On admission, the size was 7×6 cm, with fistula and pus(Fig. 1). There were hepatomegaly and splenomegaly. The laboratory data confirmed anemia and thrombocytopenia. A bone survey was performed, showing marked radiodensity in all bones, with an absence in cortico medullary demarcation and widening in the metaphyses. The long bones were bent, resulting in genu valgum in the lower extremities (Fig. 2). Her lateral spine X-ray showed dense bone near the vertebral endplates with radiolucencies at the centers of the bodies(rugby jersey spine) (Fig. 3).

The second case is of a 4-year-5 month-old girl who first came to the hospital at the age of 2 months due to brain ventricle enlargement. The patient was the older of two children. The mother underwent cesarean section for the delivery. At the age of 9 months, she received a ventriculo-peritoneal shunt for hydrocephalus (Fig. 4). At the age of 7 months, she sustained a right proximal femoral fracture after falling on the floor, the fracture was treated with closed reduction and hip spica cast. At the age of 38 months, she sustained a left distal femoral fracture after falling on the floor and was treated with closed reduction and a hip spica cast(Fig. 5). At the age of 51 months, she sustained a left tibia fracture(Fig. 6)and a left clavicle fracture after falling on the floor and was treated with closed reduction and a long leg plaster for the tibia fracture. On admission, all of these fractures had healed. At the age of 3 months, her optic nerve became non vital, and by the age of 22 months, she had developed bilateral optic atrophy. She has had hearing impairment since the age of 22 months, espe-

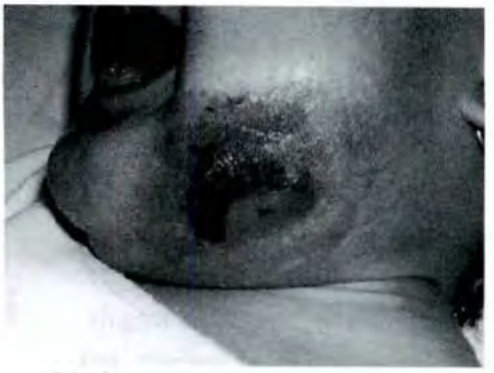

Fig. 1. Osteomyelitis in the left mandible of the first case. There is a fistula present.

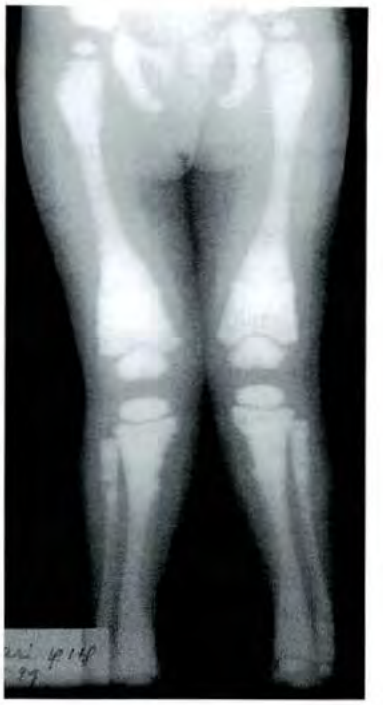

Fig. 2. The legs of the first case, showing typical osteopetrosis changes in increased bone density, and loss in the normal corticomedullary differentiation. The long bones were bent, resulting in genu valgum.

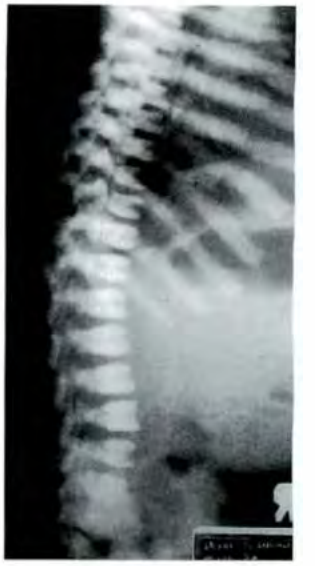

Fig. 3. The lateral spine X ray in the first case showing dense bone near the vertebral end plates and radiolucencies in the central bodies (rugby jersey spine).

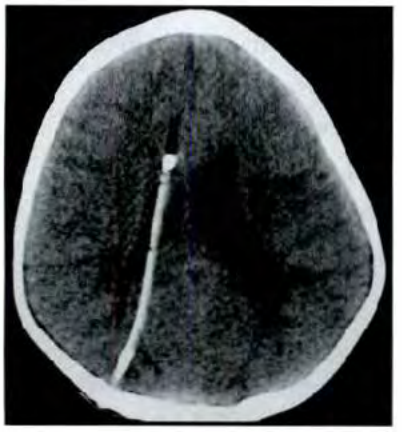

Fig. 4. Brain CT Scan in the second case, showing the ventriculo-peritoneal shunt for the treatment of hydrocephalus.

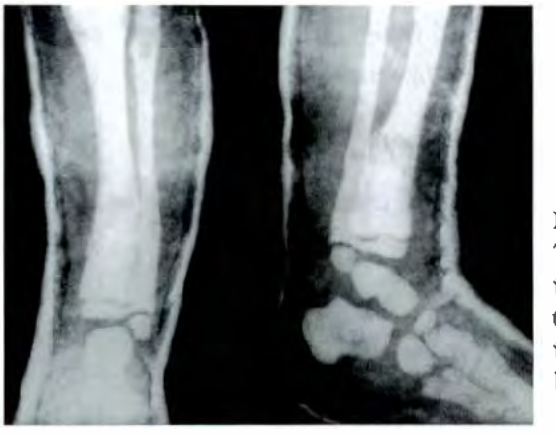

Fig. 6.
The fracture in the left tibia of the second case, treated with long leg plaster.

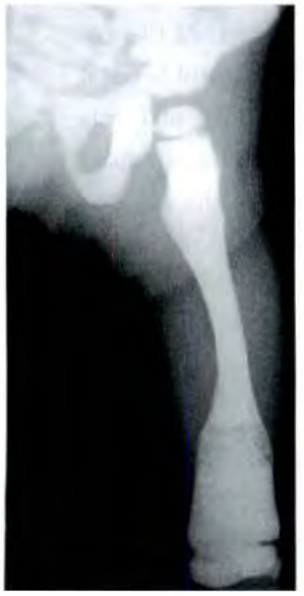

Fig. 5.
The fractured left distal femur in the second case. also showing the widened metaphyses.

cially in the right side. At the age of 53 months, she was diagnosed as having obstructive sleep apnea syndrome(OSAS). She was subsequently admitted to the Intensive Care Unit for the OSAS. She has continued to use an oropharynx tube. Laryngoscopy and nasoendoscopy examinations have found a narrowed nasopharynx

and oropharynx due to macroglossia, with permanent protrusions in the vertebrae. Computed tomographic scanning of the larynx and trachea revealed thickened in the larynx trachea muscles which had caused obliteration of the airway lumen.

Both these patients have no relatives with osteopetrosis.

Discussion

We have reported two cases of osteopetrosis. Osteopetrosis is a rare familial disease, characterized roentgenographycally by a marked increase in the radiodensity of bone and by abnormalities in the shapes of the long bones, especially the metaphyses.[1) 7)] Although genetic inheritance has been identified in some reported cases, many cases have appeared sporadically as in the present two cases.[4)] The primary underlying defect in all cases of osteopetrosis is failure of the osteoclasts to resorb bone. A number of heterogenous molecular[1)8)] genetic defects[1)9) 12)] and gene mutation[1)13)14)] can result in impaired osteoclastic function. The histological appearance of skeletal tissue and results from experimental studies are well known.[5)] Failure to reabsorb the calcified cartilage formed during endochondral ossification leads to progressive filling of the metaphyseal region, and eventually the marrow cavity in the diaphysis, with tissue composed of cores of calcified cartilage surrounded by new bone.[1)2)5)] In the most severe cases, the unresorbed tissue extends the full length and width of the bone, completely obliterating the marrow spaces and excluding the blood forming marrow cells.[1)2)5)] Failure of osteoclast to reabsorb bone at the periphery of the metaphyseal-diaphyseal junction at the distal end of Ranvier's ossification groove leads to the widened a b normally-shaped metaphyses. In the diaphysis, failure of resorption inhibits normal remodeling and cylinderization and leads to a thicker cortex.[1)2)5)] (Fig. 2, 5, 6)

In the first case, anemia, thrombocytopenia, and extramedullary hematopoiesis are manifest clinically as hepatosplenomegaly.[2)3)5)] Some have considered the hematological manifestations to be myelophthisic in nature, due at least in part to the exclusion of marrow cells by the persistent endochondral tissue. Others have considered that hemolysis and hypersplenism contributed to the anemia. A primitive disturbance in both hematopoietic and bone tissue development has been suggested.[1)3)5)]

Despite the fact that the bones are radiodense, failure in remodeling results in imperfect orientation of the collagen fibers which serves to decrease the mechanical strength, and frequent pathological fractures occur.[1)2)5)] The second case have also sustained pathological fractures since the trauma alone was not adequate to cause the fractures. We performed closed reduction and hip spica cast for the femur fracture, and long leg plaster for tibia fracture.

Osteomyelitis in the mandible is common due to an abnormal blood supply.[1)] Osteomyelitis in the mandible occurs in 10% of patients.[1)] The majority of children with osteopetrosis develop some degree of visual impairment. It is essential that all patients are assessed soon after the initial diagnosis and at regular intervals by a paediatric ophthalmologist. Clinically there is often optic atrophy although the retina is otherwise unremarkable. The visual evoked potentials (VEPs) are the most useful way of monitoring optic nerve involvement while an electror-

etinogram may help rule out associated neurological disease. The visual loss, caused by bony encroachment on the optic nerve at the optic foramina level, is progressive and almost always occurs within the first year of life. This may result in failure to establish fixation and nystagmus, or slightly later to development of strabismus.[1)3)6)] Our second case also sustained blindness and nystagmus. Hearing is less commonly affected than vision, with approximately a third of patients having some degree of hearing loss, as in our second case. The impairment usually is manifested within the first year of life. The pathology of the deafness is unclear but is probably secondary to a combination of bony compression on the nerve, sclerosis in the middle ear ossicles, and/or chronic middle ear effusion.[2)3)] Failure to thrive is seen in many osteopetrotic children, as in our cases, and is a result of the chronic anemia, feeding problems caused by bulbar nerve involvement, nasal congestion, and recurrent infections.[3)] Besides affecting the optic, facial, oculomotor and auditory nerves, overgrowth in the cranial nerve foramina and in the foramen magnum also results in hydrocephalus in osteopetrosis, as in our second case.

Hydrocephalus can be relieved by inserting a shunt, usually in the form of a ventriculo-peritoneal (VP) shunt[6)] (Fig. 4).

Some cases of osteopetrosis, as well as our second case, sustain obstructive sleep apnea syndrome (OSAS).[1)] The diagnosis was confirmed using polysomnography. The major risk factor for OSAS in children include hypertrophy in the tonsils and adenoids, neuromuscular disease including conditions associated with both muscular hypotonia and hypertonia, obesity, and genetic syndromes, especially those associated with midface hypoplasia, small nasopharynx, or micrognathia, such as Down's syndrome and Pierre Robin sequence. Less common risk factors for OSAS are laryngomalacia, pharyngeal flap surgery, sickle cell disease, structural malformations in the brain stem, and certain metabolic and genetic disorders. Viral respiratory infections and allergic rhinitis are not primary risk factors for OSAS, but they may exacerbate existing OSAS in affected children.[15)-18)] OSAS in the second case was due to circular thickening in the larynx and trachea wall and also due to a narrowed nasopharynx and oropharynx caused by macroglossia.

Bone marrow transplantation is the only treatment that has been found to alter significantly the course of disease. While successful recipients may continue to have minor orthopaedic or dental problems and their vision rarely significantly improves, their haemopoietic potential is restored and the long-term prognosis is favorable. The success of engraftment and thus outcome is very dependent however on the availability of a suitable HLA match. In 1994, Gerritsen et al. reported a 79% five-year-disease-free-survival rate in 19 patients with an HLA identical sibling donor. Recipients of non genotypically identical grafts have had significantly worse results with only a 13% five year-disease free-survival rate in those receiving marrow from an HLA haplotype mismatched related donor. A bone marrow transplant should thus be reserved for those cases where there is at least a phenotypical HLA identical match available.[3)19)-21)] Bone marrow immunoscintigraphy, by showing the extent of marrow recrudescence, may be useful in monitoring the effectiveness of therapy after transplantation.[3)] Dual

energy X-ray absorptiometry measurements have also been shown to provide accurate information on bone mineral status in young paediatric patients.[22] HLA-haploidentical blood progenitor cell transplantation has been reported in the treatment of osteopetrosis.[23] Corticostreroids, high dosage calcitriol, and interferon have been reported to be helpful in the treatment of osteopetrosis.[3][24] It is very important to counsel the patient to avoid activities that might increase the risk to fractures,[1] especially as in our second case.

Summary

Osteopetrosis is a rare congenital disorder in which the bones are overly dense. This results from an imbalance between the formation of bone and the breakdown of the bone. We have reported two cases of osteopetrosis. In the first case, osteopetrosis was complicated with osteomyelitis in the left mandible. Osteomyelitis in the mandible occurs in 10% of patients.[1] In the second case, osteopetrosis was complicated with multiple fractures, blindness, hearing impairment, hydrocephalus and OSAS.

The diagnosis of osteopetrosis in both cases was performed by typical osteopetrosis changes in increased bone density, and loss in normal corticomedullary differentiation. The treatment for osteopetrosis should be performed by specialists related to the patient's condition.

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