

OSTEOPETROSIS: EASY TO DIAGNOSE BUT DIFFICULT TO MANAGE

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ABSTRACT

Osteopetrosis is a rare and inherited skeletal disorder characterized by severe osteosclerosis due to a defect in osteoclast differentiation (osteoclast deficient) or its dysfunction (osteoclast rich). Three types of osteopetrosis have been described like congenital (autosomal recessive), intermediate or marble bone disease (autosomal recessive) and tarda (autosomal dominant). Prognosis is worst for osteopetrosis congenital, better for marble bone disease and best for osteopetrosis tarda. Treatment is primarily symptomatic with stem cell marrow transplantation for the most severe cases (autosomal recessive types) with bone marrow failure and currently offers best chance of longer survival.

Key words: Osteopetrosis; marble bone disease; Albers-Schonberg disease; bone marrow failure; bone mineral density; "Erlenmeyer flask" deformity

Introduction

The term osteopetrosis refers to a group of rare, heterogeneous inherited conditions characterized by enhanced bone density on radiographs. This is caused by defect in osteoclasts differentiation or function and mutation in at least 10 genes have been identified in about two third cases.¹ It is derived from Greek "osteo" means bone and "petros" means stone and also termed as Marble Bone Disease or Albers-Schonberg disease.² It presents in one of three forms: osteopetrosis tarda, osteopetrosis congenita and "marble bone" disease. Osteopetrosis tarda, the benign form, presents in adulthood (autosomal dominant), while the two malignant variants, osteopetrosis congenita and marble bone disease (autosomal recessive), present in infancy and

childhood, respectively.³ The incidence of autosomal recessive forms is 1 in 250,000 birth (high incidence in Costa Rica) and 5 in 100,000 births for autosomal dominant form.⁴

PATHOGENESIS: The pathogenesis of osteopetrosis warrants a better understanding of role of osteoblast and osteoclast in bone remodeling. Bone is a dynamic tissue in which osteoblasts (mesenchymal origin) synthesize bone matrix while osteoclasts (derived from hematopoietic lineage) resorb bone. Therefore, bone density is dependent on the relative function of these two types of cells. Osteoblasts synthesize bone matrix and in so doing lay down a microenvironment that supports osteoclast growth, maturation, and function. Osteoblasts also secrete macrophage colony stimulating factor (M-CSF), granulocyte macrophage colony stimulating

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factor (GM-CSF), interleukin-1, and interleukin-6, all of which influence the activities of osteoclasts. Direct interactions between osteoblasts or marrow stromal cells and osteoclast precursors are essential for the differentiation of osteoclasts.¹ Mutations in at least 10 genes have been identified responsible for osteoclast malfunction in about 70% of diagnosed cases. An important but rare defect in human is lack of carbonic anhydrase-II activity and patients with osteopetrosis will have renal tubular acidosis and cerebral calcification (Marble Brain Syndrome).⁵ Acquired osteopetrosis has been reported in patients who have been on extended phosphonate therapy. It is suggested that bisphosphonate inhibits the recruitment and function of osteoclasts and extended use of such therapy may result in a clinical picture compatible with heritable osteopetrosis.⁶

Clinical Presentation

1. Osteopetrosis Congenita (malignant osteopetrosis): This autosomal recessive form of osteopetrosis is very severe, life threatening and presents in first few months of life infancy, failure to thrive and usually results in death by the of age two years. Nerves entrapment at cranial foramina by marked osteosclerosis results in proptosis, blindness, deafness and hydrocephalus. Children are at risk of developing hypocalcemia, convulsion and secondary hypoparathyroidism. However, the most serious complication is bone marrow failure with extra-medullary hematopoiesis over liver and spleen.⁷

2. Intermediate Osteopetrosis (Marble bone disease): It is again an autosomal recessive type of osteopetrosis which is not characterized by bone marrow failure. Patients with marble bone disease are usually of short stature and present with intracranial calcifications, deafness and psychomotor retardation. Although survival rates are better for patients with marble bone disease than for patients with osteopetrosis congenita, the consequences of renal tubular acidosis may shorten life expectancy.⁸

3. Osteopetrosis tarda (benign osteopetrosis or Albers-Schonberg disease): This is an autosomal dominant type of osteopetrosis which remains asymptomatic in 50% cases and diagnosed incidentally on radiological examination. Most common presentations are fractures of brittle bones and osteomyelitis (predominantly involving mandible due to dental infection) but with normal healing process and life expectancy. These individual usually have sufficient retention of marrow cavity with normal hematopoiesis but may have an elevated acid phosphatase level.⁹

Diagnosis

The diagnosis of osteopetrosis is primarily based on clinical presentation and characteristic appearance of skeleton on radiographic imaging.

1. Plain Radiology: X-rays of all bones should be avoided due to concern of radiation exposure and reserved for atypical cases. However, films of at least one extremity, the head and the thorax should be performed to describe the morphology and extent of osteosclerosis, narrowing of medullary cavity and head deformities in the individual patient. Also check for growth plate widening as a sign of osteopetrorickets. The classic radiological features of osteopetrosis comprise:

Diffuse sclerosis, affecting the skull, spine, pelvis and appendicular bones (Fig. 1).



Figure 1

Tooth eruption defects and severe dental carries which may lead to mandibular osteomyelitis (Fig. 2).



Figure 2

Bone modeling defects at the metaphyses of long bones, such as flask-like deformity ("Erlenmeyer flask" deformity) and characteristic lucent bands (Fig.3).



Figure 3

"Bone-in-bone" appearance particularly in the vertebrae and phalanges with lucent bands in distal ulna and radius (Fig. 4).

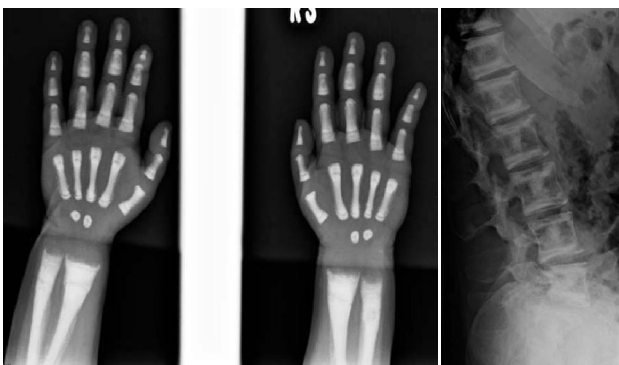


Figure 4

Focal sclerosis of the skull base, pelvis and vertebral end plates - "sandwich" vertebrae and "rugger-jersey" spine (Fig. 5).



Figure 5

2. Cross Sectional Radiology: Magnetic resonance imaging (MRI) or computerized tomography (CT) are recommended to diagnose neurological complications like hydrocephalus, narrowing of central nerve channels and atrophic changes in brain^{10,11} (Fig. 6) showing CT images with diffuse osteosclerosis and hydrocephalus)



Figure 6

3. Bone Mineral Densitometry (BMD): Dual energy X-ray absorptiometry (DXA) based measurement of BMD in osteopetrosis show abnormally high values (gm/cm square) with abnormally high T-scores and Z-scores (Z-score > +2.5¹² or T/Z-score = +4¹³) (Fig. 7). Bone densitometry has been used in osteopetrosis to observe response to bone marrow transplantation.

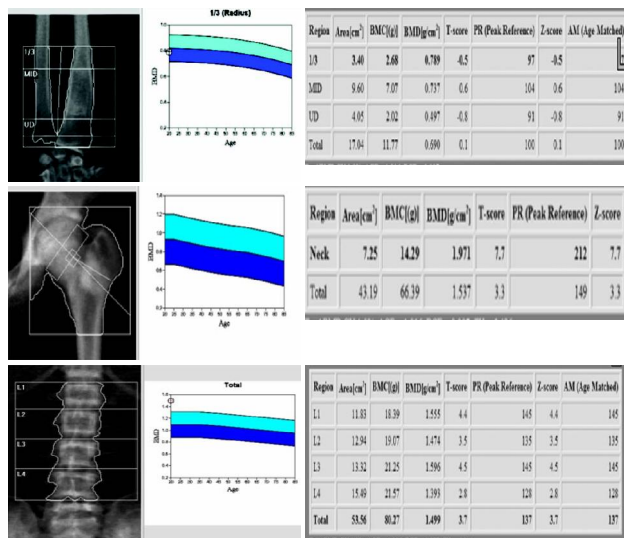


Figure 7

4. Hematology and Biochemistry: Peripheral blood films with reticulocyte count and serum LDH levels are important for assessment of bone marrow. Creatine kinase-BB isoenzyme and tartrate resistant acid phosphatase (TRAP) are helpful in diagnosis of autosomal dominant osteopetrosis. Bone metabolism parameters like serum calcium, phosphate, parathormone, alkaline phosphatase, vitamin D3 and osteocalcin are also important in ascertaining the disease status. pH of urine and blood must be measured for suspected cases of carbonic anhydrase-II defect as it is associated with renal tubular acidosis. Trepine bone marrow biopsy is done for evaluation of osteoclasts rich (but dysfunctional) or osteoclast deficient osteopetrosis and assessment of marrow status before consideration for stem cell transplantation.

Differential Diagnosis


Enhanced sclerosis is also noted in other clinical conditions as a secondary phenomenon. These include fluorosis and heavy metal (beryllium, lead and bismuth) poisoning, myelofibrosis, hyper-vitaminosis-D, Paget's disease, osteoblastic metastasis, melorheostosis (limited to one extremity) and fibrous dysplasia of skull or face.

Treatment

There is no specific treatment for osteopetrosis and largely supportive to manage the complications. Fractures are managed surgically while hypocalcemic seizures are controlled by calcium and Vit-D supplements. Bone marrow failure associated with severe autosomal recessive osteopetrosis is managed by stem cell transplantation. To facilitate bone resorption, interferon gamma has been tried with by various groups with promising results.¹⁴ Similarly, for stimulation of host osteoclasts, calcium restriction, calcitriol steroids, parathyroid hormone and interferon have also been attempted.¹⁵

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