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Mini Review

Understanding Osteopetrosis as a Rare Genetic Bone Disorder and its Multisystemic Impact

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ABSTRACT

Osteopetrosis, also referred to as Albers-Shonberg disease or marble bone disease, refers to metabolic bone diseases that adversely affect bone health and can have far reaching health implications. Osteopetrosis is a rare genetic disease that involves osteoclast dysfunction that leads to brittle bones that are susceptible to fracture. There are 4 forms of the condition, each of which manifests differently and is managed differently. Here, we summarize the latest in what is known about osteopetrosis and its management.

Keywords: Osteopetrosis; Fracture; Trauma; Health; Joint; Muscle

INTRODUCTION

Osteopetrosis, also known as Albers-Schonberg disease, refers to a heterogenous group of hereditary metabolic bone diseases that have a negative impact on bone growth and bone health [1-3]. As the name implies, with 'osteo' meaning bone and 'petrosis' meaning stone, diseases of this category are characterized by abnormally high bone density, making the bone brittle and susceptible to fractures [4,5]. The disease was first systematically described in 1904 when it was referred to as 'marble bone disease' [5,6]. However, written reports suggest the disease has been recognized as far back as 350 A.D [7]. Here we summarize the incidence and pathophysiology of osteopetrosis, its complications and how it is diagnosed and treated.

OSTEOPETROSIS IS A GENETIC DISEASE OF OSTEOCLAST DYSFUNCTION

Osteopetrosis is rare and linked to mutations in several genes that influence the functions of osteoclasts, which breakdown bone [7-9]. Without proper osteoclast function, bone resorption is hindered, causing an imbalance in the rate at which bone is formed and broken down [1,10,11]. The result is a disorganized pattern of cortical bone deposition in those with osteopetrosis, making bones brittle and more prone to fracture as shown in Figure 1, marbleized, cancellous bone chips [7]. The disordered architecture of the bones is also accompanied by sclerosis. Research suggests that osteoblasts are also implicated in osteopetrosis, though the mechanisms by which osteoblasts contribute to the disease are unclear [12].

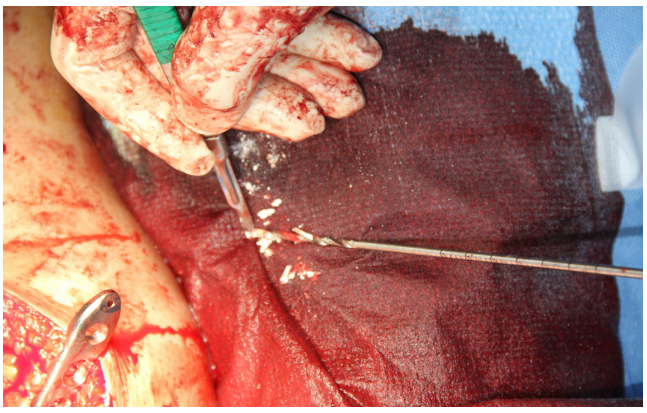

Figure 1: Marbleized cancellous bone chips.

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There are 4 forms of osteopetrosis, named for their combination of severity and pattern of inheritance. They include type I autosomal dominant, type II autosomal dominant, intermediate autosomal recessive, and malignant autosomal recessive [7]. These forms occur at different rates in the population. While approximately 1 in every 20,000 births results in the autosomal dominant form of osteopetrosis, only about one in every 250,000 births occur in the autosomal recessive form [7].

The form of osteopetrosis dictates the mechanisms of osteoclast dysfunction as well as the clinical presentation and prognosis. For instance, one genetic mutation may impact osteoclast differentiation while another may influence vesicle trafficking [1,11]. Those with the autosomal recessive forms of osteopetrosis often die in childhood from bleeding, secondary infections, or multi-organ failure, while those with autosomal dominant forms may have no reduction in life expectancy despite suffering significant orthopedic challenges [13-20].

DIAGNOSIS DEPENDS ON CLINICAL PRESENTATION AND RADIOGRAPHIC FINDINGS

In most cases, patients with osteopetrosis present with fractures, which are often transverse and involve callus formation in multiple areas [3,21]. The medullary canal is lost in bones that lack osteoclast activity, leaving the end of long bones bulbous, with a characteristic metaphyseal flare, often referred to as Erlenmeyer flask deformity as demonstrated in Figures 2 and 3 [22,23].

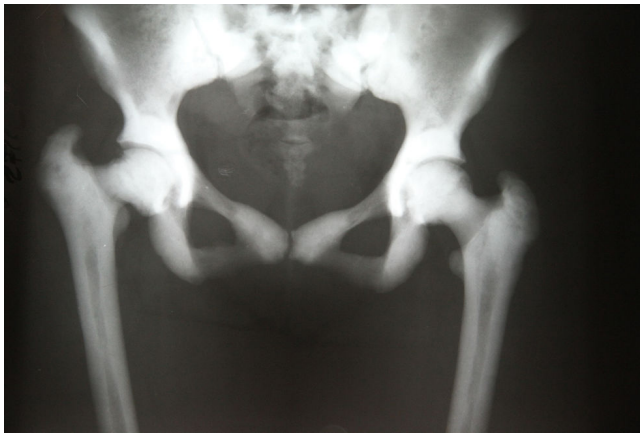

Figure 2: Radiographic findings showing diffused bilateral narrowing of the intramedullary canals. Blastic activity involving the iliac bones and the sacral ala is also observable. Patient demonstrates right femoral neck fracture with varus deformity.

Marrow crowding is common in osteopetrosis, adversely affecting bone marrow function. Because there is no space for hematopoietic tissue, the development of anemia and extramedullary hematopoiesis with hepatosplenomegaly may occur [24]. Patients therefore often suffer cranial nerve compression, which can lead to a variety of symptoms [25].

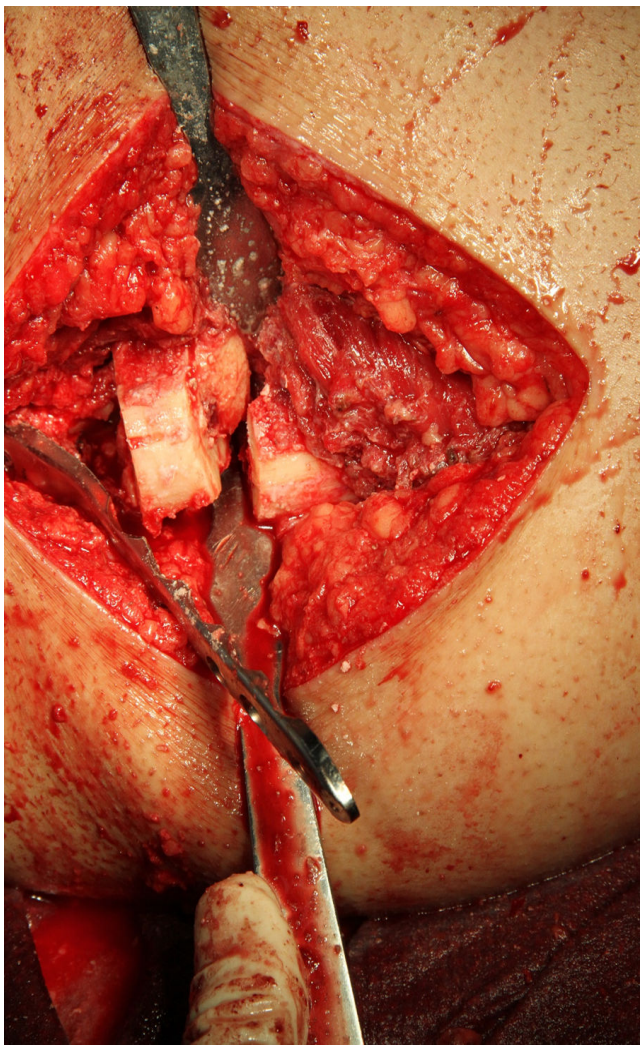

Figure 3: Cross-section demonstrates marked narrowing of medullary canal, consistent with osteopetrosis.

Each form of osteopetrosis presents differently and each can be difficult to diagnose and treat [7]. However, clinical and radiographic findings usually prompt bone biopsy and genetic testing that lead to an osteopetrosis diagnosis [5]. While radiographic findings are recommended for diagnosis, genetic testing can provide critical information on mutations that are predictive of specific disease complications [26].

OSTEOPETROSIS MANIFESTS AS MORE THAN JUST A BONE DISEASE

Patients with osteopetrosis tend to endure pathological fractures and are increased risk for skeletal abnormalities such as dwarfism and osteosclerosis [5,7,13,17]. In addition to bone fragility and bone deformities, they experience other complications at higher rates than the general population as well.

Neurological disorders

Osteopetrosis heightens the risk for neurological conditions due to the compression of cranial nerves and cranial nerve entrapment [5,11,13,14,27]. Optic atrophy, blindness, auditory deficits including deafness, facial nerve palsy and neuralgia are common complications of Osteopetrosis [12,25,28-31].

Rapid neurodegeneration in those with autosomal recessive osteopetrosis is often accompanied by seizures [19,20]. Ischemic events may occur in those with osteopetrosis as a result of stenosis of blood vessels and spinal cord compression can lead to quadriplegia and paraparesis [25,29,32-34]. Children with osteopetrosis also commonly present with hydrocephalus and symptoms of intracranial hypertension that result from cerebrospinal fluid pathway obstruction [25,29,30].

Blood disorders

Osteopetrosis is associated with anemia and other hematological challenges including pancytopenia and thrombocytopenia, which occur due to malfunctioning bone marrow [12,17,18,35]. Hematological failure can result when osteopetrosis prevents bone cavity enlargement, thereby impairing bone marrow development [12]. Without sufficient bone marrow, normal blood cell formation is limited.

Immune dysfunction

Osteopetrosis increases the risk of infection because those with the condition suffer compromised immune function [17]. Given that osteoclasts play a role in immune modulation, and some research suggests that impairments in phagocytic cell function and NK cell activity deficits may contribute to reduced immunity in those with Osteopetrosis [36-40].

Other complications

Several other complications are also observed in osteopetrosis, including dental deformities, skin lesions, renal tubular acidosis, nasal obstruction and short stature [17,41-44].

TREATMENT OF OSTEOPETROSIS DEPENDS ON THE FORM OF THE DISEASE

Early diagnosis is critical for effective intervention, particularly in more severe forms of Osteopetrosis [2,11]. However, the specific approach to osteopetrosis treatment depends on the severity of any given patient's condition as well as their symptoms [5].

Infantile-malignant osteopetrosis

Infantile-malignant osteopetrosis is treated with allogenic bone marrow transplantation, which is the only treatment that can cure the condition, thereby improving life expectancy [45,46].

Severe osteopetrosis

Many of those with severe forms of osteopetrosis pursue Hematopoietic Stem Cell Transplantation (HSCT), which provides osteoclast precursors to the body and can restore bone metabolism [1,2,9-11,13,47,48]. Patients with Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) deficiency are not good candidates for HSCT and thus may undergo RANKL replacement therapy or other forms of intervention [1]. Treatments that target RANKL are also used to prevent hypercalcemia in those who have undergone HSCT.

Less severe osteopetrosis

Consensus guidelines for osteopetrosis treatment for those with less severe forms of osteopetrosis focus on monitoring for complications and for mineral metabolism changes and providing supportive therapy where appropriate [26,49]. High doses of calcitriol are not recommended for these patients [26].

There is also ongoing research into experimental approaches to treating osteopetrosis, such as gene correction of Inducible Pluripotent Stem Cells (iPSCs), protein replacement, non-genotoxic myeloablation, lentiviral-based gene therapy, prenatal treatment and RNA interference [50]. These innovative therapeutic advancements are improving our ability to provide targeted therapies that more precisely address the specific needs of individual patients.

CONCLUSION

Though osteopetrosis is a disease of osteoclast dysfunction, it is associated with clinical complications that extend well beyond the bone to the brain, blood and immune system. A combination of clinical and radiological findings tends to prompt the biopsy and genetic testing that lead to diagnosis. However, the management of the disease varies significantly, depending on clinical manifestations, severity, and prognosis, all of which result in part on the basis of the patient's pattern of heredity. While people with less severe forms of osteopetrosis may live normal lives with regular clinical monitoring, those with more severe forms of the disease may pursue rigorous treatments such as stem cell transplantations to boost osteoclast functioning and mitigate symptoms associated with their disease. Though there is no cure for osteopetrosis, advances in therapy are now providing more options for patients suffering from the disease.

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