SYNDROMES

Marble bone disease

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Introduction

Albers-Schönberg first reported osteopetrosis in 1904 in an adult patient with generalized bone sclerosis and multiple fractures. Osteopetrosis is a heterogeneous group of inherited bone remodeling disorders in which there is a defect in bone resorption by osteoclasts. The disease is associated with an increase in skeletal mass due to abnormally dense bone. The decrease in osteoclastic activity also affects the shape and structure of the bone. Abnormal remodeling of primary woven bone to lamellar bone results in brittle bone that is prone to fracture.

The clinical manifestations and prognosis vary depending on the classification and genetic features. In severely affected patients, the medullary cavity is filled with new bone leaving little space remaining for haematopoietic cells, leading to a number of haematological and metabolic abnormalities. Neurological sequelae are common in osteopetrosis, particularity auditory and optic nerve dysfunction. Canal stenosis can lead to blindness and deafness. In addition facial nerve paralysis, developmental delay, and mental retardation can occur.

Orthopaedic problems relevant to all clinical variants include pathological fractures, coxa vara, long-bone bowing, back pain, arthritis and osteomyelitis.

Epidemiology and genetics

The human variants of osteopetrosis can be categorized as:

1. Infantile autosomal recessive.
2. Intermediate autosomal recessive.
3. Autosomal dominant (further divided into autosomal dominant I and II).

The condition is rare; incidences have been reported at 1 in 20,000–500,000 for the dominant form and 1 in 200,000 for the recessive forms.

The infantile autosomal recessive form of osteopetrosis is most commonly diagnosed soon after birth or within the first few years of life, with symptoms of infection, haemorrhage, or profound anaemia. The condition worsens rapidly and in the absence of effective medical intervention, leads invariably to death in the first few years. Balemans et al. report that 75% of untreated patients die by the age of 4 years as a consequence of associated complications.

Intermediate autosomal recessive osteopetrosis is a milder form of the condition; more commonly diagnosed towards the end of the first decade of life, and not following the malignant course. Often fracture brings about diagnosis due to the characteristic radiograph features of increased density and decreased metaphyseal remodeling.

Other associated findings include:

- Mild disproportionate short stature.
- Macrocephaly.
- Recurrent fractures.
- Osteomyelitis.
- Mild anaemia.
The autosomal dominant form is the most benign variant of osteopetrosis and is not associated with shortened lifespan. Almost half of patients diagnosed with this condition are asymptomatic. The major symptom is pathological fractures, found in approximately 40% of patients. Such fractures are often transverse. Bone pain, especially in the lumbar area, is reported in 25% of patients.⁸

Radiological appearance

The diagnosis of osteopetrosis is radiological, supported by computerized tomography if necessary. Global features are of a generalized symmetrical sclerosis and metaphyseal widening.

The clinical manifestations as diagnosed by radiograph in infantile autosomal recessive osteopetrosis are a significant increase in skeletal bone mass resulting in total or near-total obliteration of the bone marrow cavity (Fig. 1A and B). Bones can appear short and broad or long and thin. The entire skull is usually involved in infantile osteopetrosis, with the base of the cranium being the most severely affected.⁹

Pathological fractures are the main presenting feature of intermediate autosomal recessive osteopetrosis. Radiologically patients may have a disproportionately short stature, dental abnormalities, and evidence of a chronic osteomyelitis.¹⁰ The metaphyses are wider and failure of remodeling is seen especially in the distal femora as the “Ehrlenmeyer flask” deformity. In some patients the endobones can be seen.

In 1987, Anderson and Bollerslev divided the autosomal dominant form radiologically into two distinct types. In Type I, sclerosis of the skull mainly affects the vault and was associated with marked calvarial thickening (Fig. 1C). In contrast Type II, sclerosis was found in the base of the skull. Thickening and sclerosis of vertebral endplates (rugger jersey spine, Fig. 1D) is always present.¹¹

Other bony defects have been reported such as frontal bossing and genu valgum. The appearance of “bone within bone” is most characteristic of adult osteopetrosis, and is an unusual finding in the infantile form.¹⁰

Biochemical markers

Early diagnosis of the condition is important for the subsequent management of the affected patients. A recent study investigated the correlation of serum creatine kinase (CK) isoenzyme patterns, specific biochemical markers of bone metabolism and cytokines in correlation with the pathophysiology of osteopetrosis.¹² Serum CK-BB of the patient was found to be elevated to 18.0% (normal 1.67–7.6%) and biochemical markers of bone resorption were decreased. These markers may be used to differentiate osteopetrotic patients from other sclerosing bone diseases. If used for prenatal diagnosis early bone marrow transplantation can be planned ahead and possibly result in a better chance of survival.

Orthopaedic manifestations

Fractures

Fractures are common and are one of the classical features of osteopetrosis. The long bones are most frequently affected and fractures tend to occur only after moderate trauma. Two types of fracture are seen in children with infantile osteopetrosis. These are either diaphyseal or metaphyseal fractures that are generally transverse and minimally displaced. There is a high incidence of hip and proximal femoral fractures in the autosomal dominant group. These can undergo successful internal fixation, although extreme hardness of the bone makes intervention difficult.¹³ Fractures heal, although the time to healing is often prolonged. Chhabra et al. report drill flutes being immediately filled by

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bone and hence rendering the drill ineffective, and generation of significant frictional heat resulting in breakage of the drill, hence highlighting the importance of preoperative planning, patience and caution required.\textsuperscript{14}

\textbf{Coxa vara}

Many patients develop coxa vara deformity, some in the first few years of life. This deformity is seen in the intermediate and autosomal dominant forms and is the most common deformity in these specific groups.\textsuperscript{9} The coxa vara deformity appears to be caused by stress fractures in the femoral neck, with gradual deformity ensuing. The deformity can be treated by osteotomy, but can be complicated by difficulty with fixation, delayed healing, non-union and recurrent deformity.\textsuperscript{7}

\textbf{Long bone deformity}

Other long bone deformity is occasionally seen in autosomal dominant osteopetrosis. There is lateral bowing, usually involving the femur, or more rarely the tibia, humerus, radius and ulna. This deformity may be secondary to malunion after diaphyseal and metaphyseal fractures.\textsuperscript{9}

\textbf{Osteomyelitis}

Due to diminished vascularity of the bones and impaired white cell function, osteomyelitis is frequently seen with osteopetrosis. The most common site of involvement is the mandible.\textsuperscript{15} The teeth are generally impaired and are prone to become carious.\textsuperscript{9} Long bone infections also occur and once established in patients are difficult to eradicate.

\textbf{Back pain}

Back pain is most frequently reported in cases of benign autosomal dominant osteopetrosis. This rarely requires surgical intervention, but can be persistent requiring bracing and medication regimens. Associated spondylolysis or scoliosis has been described, but the majority of cases present with no structural abnormality.\textsuperscript{10}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image1.png}
\caption{(A) Distal femur showing bone within bone appearance; (B) upper arm showing sclerotic bones and loss of cortiomedullary differentiation; (C) marked calvarial thickening; and (D) rugger jersey spine.}
\end{figure}
Osteoarthritis

Degenerative arthritis of the hip and knee is seen with increased frequency in mid-adult life in patients with the autosomal dominant form. It is theorized that increased stiffness of the dense subchondral bone predisposes to premature cartilage degeneration. Total hip and knee arthroplasties have been performed with good results, but technical difficulties can be encountered during reaming, cementing and implanting due to the extremely hard bone and narrow or absent intramedullary canals. The use of instruments made from tungsten carbide has allowed successful treatment for demanding cases, such that it has been recommended that in elective surgery it is mandatory that specialist equipment is available. The technical difficulty during total hip arthroplasty due to the absence of the femoral canal can be avoided by resurfacing arthroplasty. However special equipment (and screws) might be needed.

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References