Osteopetrosis

Osteopetrosis is a descriptive term that refers to a group of rare, heritable disorders of the skeleton characterized by increased bone density on radiographs. The overall incidence of these conditions is difficult to estimate but autosomal recessive osteopetrosis (ARO) has an incidence of 1 in 250,000 births, and autosomal dominant osteopetrosis (ADO) has an incidence of 1 in 20,000 births. Osteopetrotic conditions vary greatly in their presentation and severity, ranging from neonatal onset with life-threatening complications such as bone marrow failure (e.g., classic or "malignant" ARO), to the incidental finding of osteopetrosis on radiographs (e.g., osteopoikilosis). Classic ARO is characterised by fractures, short stature, compressive neuropathies, hypocalcaemia with attendant tetanic seizures, and life-threatening pancytopenia. The presence of primary neurodegeneration, mental retardation, skin and immune system involvement, or renal tubular acidosis may point to rarer osteopetrosis variants, whereas onset of primarily skeletal manifestations such as fractures and osteomyelitis in late childhood or adolescence is typical of ADO. Osteopetrosis is caused by failure of osteoclast development or function and mutations in at least 10 genes have been identified as causative in humans, accounting for 70% of all cases. These conditions can be inherited as autosomal recessive, dominant or X-linked traits with the most severe forms being autosomal recessive. Diagnosis is largely based on clinical and radiographic evaluation, confirmed by gene testing where applicable, and paves the way to understanding natural history, specific treatment where available, counselling regarding recurrence risks, and prenatal diagnosis in severe forms. Treatment of osteopetrotic conditions is largely symptomatic, although haematopoietic stem cell transplantation is employed for the most severe forms associated with bone marrow failure and currently offers the best chance of longer-term survival in this group. The severe infantile forms of osteopetrosis are associated with diminished life expectancy, with most untreated children dying in the first decade as a complication of bone marrow suppression. Life expectancy in the adult onset forms is normal. It is anticipated that further understanding of the molecular pathogenesis of these conditions will reveal new targets for pharmacotherapy.

Disease name and synonyms

The term osteopetrosis is derived from the Greek, 'osteo' meaning bone and 'petros', stone. Osteopetrosis is variably referred to as 'marble bone disease' and 'Albers-Schönberg disease', after the German radiologist credited with the first description of the condition in 1904 [1].

Definition and classification

Osteopetrosis comprises a clinically and genetically heterogeneous group of conditions that share the hallmark of increased bone density on radiographs. The increase in bone density results from abnormalities in osteoclast differentiation or function. The Nosology Group of the International Skeletal Dysplasia Society classifies increased bone density conditions into several distinct entities based on clinical features, mode of inheritance and underlying molecular and pathogenetic mechanisms (Table 1) [2].

Table 1
### Epidemiology

These conditions are rare, and their overall incidence is difficult to estimate. Autosomal recessive osteopetrosis has an incidence of 1 in 250,000 births, with a particularly high incidence reported in Costa Rica (3.4:100,000) [3]. Autosomal dominant osteopetrosis has an incidence of 5:100,000 births [4].

### Clinical descriptions

Osteopetrosis encompasses a group of highly heterogeneous conditions, ranging in severity, from asymptomatic to fatal in infancy.

The increased bone mass can result in phenotypic features such as macrocephaly and altered craniofacial morphology, but more importantly impacts on other organs and tissues, notably the bone marrow and nervous systems. The key clinical manifestations, onset, severity, treatment, prognosis and recurrence risks for the main types of osteopetrosis are summarised in Table 2.

### Table 2

Summary of the key clinical manifestations, onset, severity, treatment, prognosis and recurrence risks of the main types of osteopetrosis
### Osteopetrosis | Orphanet Journal of Rare Diseases | Full Text

**5% of individuals.**

particularly affecting the mandible in association with dental abscess or caries

**bands of sclerosis parallel to the vertebral endplates – Figure**

**Autosomal dominant osteopetrosis (Albers-Schönberg disease)**

**syndrome (LAD-III) also suffer from severe osteopetrosis**

**Common variable immune deficiency (CVID) has been described in association with a particular subtype of osteoclast-poor ARO**

**The presence of severe immunodeficiency with ectodermal changes is observed in**

**short stature, dental abnormalities, cranial nerve compression and developmental delay**

**ARO with renal tubular acidosis (RTA)**

containing lysosomes in Schwann cells

**heterotopias**

**lysosomal storage disorder**

**delay, hypotonia, retinal atrophy with absent evoked visual potentials and sensorineural deafness**

**ARO variants**

**sites such as the liver and spleen.**

**suppression. The abnormal expansion of bone interferes with medullary haematopoiesis, resulting in life-threatening pancytopaenia, and secondary expansion of extramedullary haematopoiesis,**

**Hypocalcaemia**

**Pancytopaenia.**

**Hydrocephalus**

**Hypocalcaemia**

**Pathological fractures**

**Osteomyelitis**

**Dental abnormalities: tooth eruption defects and dental caries**

**increased bone density, diffuse and focal sclerosis of varying severity**

**Modelling defects at metaphyses**

**Cranial nerve compression.**

**Bone marrow impairment rare.**

**As for classic ARO, but primary neurodegeneration, including retinal atrophy**

**Renal tubular acidosis.**

**Developmental delay, Intracranial calcification.**

**Anhidrotic ectodermal dysplasia.**

**Anaemia and extramedullary haematopoiesis.**

**Immunodeficiency resulting in overwhelming infection.**

**Occasional optic nerve compression.**

**Cranial nerve compression**

<table>
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<tr>
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<th>Skeletal</th>
<th>Other</th>
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**Autosomal recessive (“malignant”) osteopetrosis (ARO)** is a life-threatening condition, which classically manifests in the first few months of life. The increase in bone density can paradoxically weaken the bone, resulting in a predisposition to fractures and osteomyelitis. The longitudinal growth of bones is impaired, resulting in short stature of varying degrees. Macrosephaly and frontal bossing develop within the first year, resulting in a typical facial appearance. The skull changes can result in choanal stenosis and hydrocephalus.

**Pathological fractures**

**Osteomyelitis**

**Cranial nerve compression**

**Bone marrow impairment rare.**

**As for classic ARO, but primary neurodegeneration, including retinal atrophy**

**Renal tubular acidosis.**

**Developmental delay, Intracranial calcification.**

**Hypotonia.**

**Retinal atrophy with absent evoked visual potentials.**

**Sensorineural deafness.**

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**sites such as the liver and spleen.**

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**Autosomal recessive (“malignant”) osteopetrosis (ARO)** is characterised by seizures in the setting of normal calcium levels, developmental delay, hypotonia, retinal atrophy with absent evoked potentials and sensorineural deafness. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Reported brain MRI findings include significantly delayed myelinisation, diffuse progressive cortical and subcortical atrophy, and bilateral atrial subependymal heterotopias. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells.

**Renal tubular acidosis (RTA)** has a milder course where RTA and cerebral calcifications are typical. Other clinical manifestations comprise increased frequency of fractures, short stature, dental abnormalities, cranial nerve compression and developmental delay.

The presence of severe immunodeficiency with ectodermal changes is observed in X-linked osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia and immunodeficiency (OLEDAD) syndrome (LAD-III) also suffer from severe osteopetrosis.

Common variable immune deficiency (CVID) has been described in association with a particular subtype of osteoclast-poor ARO, and some patients with leukocyte adhesion deficiency syndrome (LAD-III) also suffer from severe osteopetrosis.
**ADO: lateral spine radiograph, age 4 years.** Note sclerosis of vertebral endplates (arrows) resulting in ‘sandwich vertebra’ appearance.

*Pycnodysostosis* was first described by Maroteaux and Lamy in 1962 [16], and there is evidence that the French painter Henri de Toulouse-Lautrec [17] and the ancient Greek author Aesop [18] were afflicted by this condition. Pycnodysostosis is characterised by short stature, increased bone fragility, persistent open anterior fontanelle and acro-osteolysis of the terminal phalanges (Figure 2). The typical ‘open mouth outline’ facial appearance is due to frontal bossing, micrognatia, loss of the mandibular angle (Figure 3), and dental anomalies including persistence of deciduous teeth resulting a double row of teeth [19, 20]. Other reported manifestations include joint hypermobility, obliteration of frontal and other sinuses [21], pituitary hypoplasia, cerebral demyelination [22], and hepatosplenomegaly [23].
Pycnodysostosis: Hand radiograph, age 3 years. Note acro-osteolysis in the distal phalanx of thumb and index fingers (arrows) and generalised increased bone density.

Pycnodysostosis: Lateral skull radiograph, age 3 years. Note loss of the mandibular angle (arrow) and increased thickness of vault.

Dysosteosclerosis was first described as a separate condition in 1968 \[^{24}\] and is marked by the presence of skin changes (red-violet spots in a patchy distribution), developmental regression and an overall poor prognosis. It manifests in infancy and can be distinguished from other osteopetrotic conditions by platyspondyly, bowing of the long bones, and the lack of bone marrow involvement or acro-osteolysis \[^{25}\]. Typically, the expanded areas of bone are relatively radiolucent, in contrast to the sclerosis of expanded areas seen in ARO \[^{25}\].

Osteopoikilosis is a benign, usually asymptomatic condition diagnosed radiographically by the presence of multiple symmetrical circular/ovoid sclerotic opacities of the ischiae, pubic bones and the epimetaphyseal regions of the short tubular bones. Osteopoikilosis can occur in isolation, or in association with elastic or collagen connective tissue naevi of the skin, a condition termed Buschke-Ollendorff syndrome (BOS). Both osteopoikilosis and BOS are inherited in an autosomal dominant pattern. In some families and individuals, osteopoikilosis can also occur in association with melorheostosis \[^{26},^{27},^{28},^{29}\]. Melorheostosis is usually a sporadic sclerosing bone condition manifesting in a sclerotomal distribution, frequently affecting one limb. There is cortical hyperostosis with thickening, which resembles dripping candle wax on radiographs. Melorheostosis can be asymptomatic or if severe can result in pain, stiffness, leg-length discrepancy and deformity.

Osteopathia striata (OS) occurs in isolation or with cranial sclerosis (OS-CS). The key feature is longitudinal striation of the metaphyses of the long bones \[^{30}\]. OS-CS in particular is a clinically heterogeneous condition, ranging from mild skeletal manifestations to multisystem organ involvement even within the same family \[^{31}\]. The typical clinical features include macrocephaly, cleft palate and hearing loss; additional features including cardiac malformations, developmental delay, cranial nerve palsies, anal malformations, cataracts and nervous system malformations have been reported.

**Aetiology**

Osteopetrosis is caused by failure of osteoclast differentiation or function \[^{1}\]. The pathogenesis of osteopetrosis is best understood with reference to normal osteoclast development and function (Figure 3).
Osteoclasts are highly specialised cells, which degrade bone mineral and organic bone matrix. These processes are crucial for bone remodelling and the maintenance of bone biomechanical stability and mineral homeostasis. It is estimated that the adult skeleton is completely regenerated every 10 years [1, 2]. Osteoclasts are derived from the mononuclear precursors in the myeloid lineage of haematopoietic cells that also give rise to macrophages [3, 4]. The osteoclast precursors fuse, resulting in osteoclasts, which typically have 5-8 nuclei. By contrast, osteoblasts are derived from multipotent mesenchymal stem cells, which also give rise to chondrocytes, adipocytes and muscle cells.

In light of the common origin of osteoclasts and cells of the haematopoietic system, it is not surprising that mutations in molecules such as IKBKG (NEMO) [5, 6], Op/op mice which do not express functional M-CSF lack osteoclasts and have osteopetrosis [7], however human patients with osteopetrosis secondary to M-CSF deficiencies are yet to be identified. Recently a kindred with RANKL gene mutation [8] and seven families with RANK gene mutation [9, 10] and osteopetrosis have been described.

A fully differentiated osteoclast dissolves bone mineral and degrades bone matrix using specialised enzymes. Crucial to this function is cell polarisation, and in particular the formation of the ruffled border and sealing zone. These form the resorption lacuna where hydrochloric acid is actively secreted resulting in the dissolution of bone mineral hydroxyapatite.

Most forms of osteoclast-rich osteopetrosis are caused by defects in gene products involved in the acidification machinery. Acid secretion is dependent on two key molecules, which facilitate proton transport: the proton pump vacuolar ATPase (V-ATPase) and the chloride-specific ion channel, chloride channel 7 (CLCN-7) [11]. Homozygous mutations in the genes encoding the a3 subunit of V-ATPase (TCIRG1) and the CLCN-7 produce severe malignant osteopetrosis phenotypes in both humans and mice [12, 13, 14, 15]. TCIRG1 mutations are responsible for autosomal recessive osteopetrosis in more than 50% of affected individuals [16, 17] underscoring the crucial role of V-ATPase in osteoclast function. CLCN-7 on the other hand plays a key role in lysosomal acidification, which explains the severe neuronal storage and neurodegeneration in the CNS and retina in Clcn7-/- mice and in a subset of human ARO patients [18, 19]. Dominant-negative mutations of CLCN-7 have been shown to cause ADO [20, 21]. CLCN-7 is closely associated with another membrane protein, OSTM1 [22]. Mutations in the OSTM1 gene are found in grey-lethal mice and a subset of ARO patients with neurological involvement [23, 24].

The protons and chloride ions that are expended in the acidification process need to be replenished intracellularly in order to avoid alkalinization. This is achieved by carbonic anhydrase type II (CAII) and an anion exchanger. Given the key role of CAII in kidney function, it is not surprising that mutations in CAII result in ARO with tubular acidosis [25].

lysosomal acidification, which explains the severe neuronal storage and neurodegeneration in the CNS and retina in Clcn7-/- mice and in a subset of human ARO patients [18, 19]. Dominant-negative mutations of CLCN-7 have been shown to cause ADO [20, 21]. CLCN-7 is closely associated with another membrane protein, OSTM1 [22]. Mutations in the OSTM1 gene are found in grey-lethal mice and a subset of ARO patients with neurological involvement [23, 24].

The collagen bone matrix is dissolved by two groups of enzymes, the matrix metalloproteinases (MMPs) and lysosomal cathepsins. Cathepsin K in particular has been identified as a key enzyme. It is secreted in the resorption lacuna [26, 27] where it degrades collagen I at acidic pH. Inhibition of cathepsin K prevents matrix degradation [28, 29], and deletion of the cathepsin K gene in mice leads to osteopetrosis [30, 31]. Homozygous mutations in the human cathepsin K gene lead to pycnodysostosis [32].

The formation and maintenance of the osteoclast polarised membrane domains requires complex vesicular trafficking mechanisms and continuous remodelling of the osteoclast cytoskeleton. One such protein, which plays a critical function in vesicle trafficking and acidification is PLEKHM1, and heterozygous mutations in this have been associated with intermediate forms of osteopetrosis [33].

Other signalling pathways are likely to be important in osteoclast function, and mutations in the LEMD3 gene which codes for an integral protein of the inner nuclear membrane thought to be involved in BMP and TGFβ signalling, result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis [38, 39]. WNT-related signalling defects (of PORCN [60, 61] and WTX [62] genes) have recently been associated with hyperostotic phenotypes (osteopathia striata in Goltz syndrome and Osteopathia Striata with Cranial Stenosis, OSCS, respectively) implying a role for the WNT pathway in osteoclast function.

Mutations in genes described so far only account for approximately 70% of cases. The field of osteopetrosis research has benefited from the many naturally occurring rodent models of the disease. Many genetic defects observed in rodents have not been observed in humans, and these form natural targets for future studies.

**Diagnosis**

The mainstay of diagnosis is clinical and largely depends on the radiographic appearance of the skeleton. The classic radiological features of osteopetrosis comprise:

- **Diffuse sclerosis, affecting the skull, spine, pelvis and appendicular bones.**
- **Bone modelling defects at the metaphyses of long bones, such as funnel-like appearance (*Erlenmeyer flask* deformation) (Figure 3), and characteristic lucent bands (Figure 6).**
ADO: Radiograph of left femur, age 4 years. Note Erlenmeyer flask deformity of distal femur (arrows) and generalised increased bone density.

Severe ARO: Right hand radiograph, age 2 weeks. Note metaphyseal lucent bands in the distal ulna and radius (arrows) and short tubular bones.

*"Bone-in-bone" appearance particularly in the vertebrae and phalanges.
Osteopetrosis is a trait that can be inherited. If the mother of the proband is a carrier, 50% of male pregnancies will be affected, and 50% of female pregnancies will be carriers. Given the low incidence of osteopetrosis in the general population, the risk that the proband or their siblings would have affected children is low.

Autosomal dominant: the parents of the proband should be carefully evaluated for signs of osteopetrosis, including radiographic studies of the skeleton. Each child of an affected individual has a 1 in 2 (50%) risk of being affected. If the parents are unaffected, there may still be a low risk of further affected children due to gonadal mosaicism.

X-linked recessive: if the mother of the proband is a carrier, 50% of male pregnancies will be affected, and 50% of female pregnancies will be carriers. If the mother is not a carrier, there may still be a small risk of further affected offspring due to gonadal mosaicism.

Once the diagnosis of a primary osteopetrotic condition is made, it is important to distinguish between different subtypes as they have different response to treatment, prognosis and recurrence risks.

Differential diagnosis

Primary sclerosing conditions of bone caused by osteoclast dysfunction need to be distinguished from the large number of conditions in which bone sclerosis can occur as a secondary phenomenon. Some alternative diagnoses to consider include fluorosis, beryllium, lead and bismuth poisoning; myelofibrosis; Paget’s disease (sclerosing form); and malignancies (lymphoma, osteoblastic cancer metastases). Neonatal radiographs can be particularly difficult to interpret in the absence of additional multiorgan involvement, as the normal neonatal skeleton can appear denser than normal. However, in contrast to osteopetrosis, this appearance will improve over time.

Once the diagnosis of a primary osteopetrotic condition is made, it is important to distinguish between different subtypes as they have different response to treatment, prognosis and recurrence risks.

Genetic counselling

The severe infantile forms of osteopetrosis are associated with diminished life expectancy, with most untreated children dying in the first decade as a complication of bone marrow suppression. Life expectancy in the adult onset forms is normal.

Prognosis

The severe infantile forms of osteopetrosis are associated with diminished life expectancy, with most untreated children dying in the first decade as a complication of bone marrow suppression. Life expectancy in the adult onset forms is normal.

Declarations

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Below are the links to the authors’ original submitted files for images.

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Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Both authors read and approved the final manuscript.

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