

Autosomal recessive osteopetrosis

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[Abstract](#)

[Keywords](#)

[Disease name / synonyms](#)

[Excluded Diseases](#)

[Diagnosis criteria /definition](#)

[Differential diagnosis](#)

[Incidence](#)

[Clinical Description](#)

[Management including treatment](#)

[Outcome](#)

[Etiology](#)

[Genetics Counseling](#)

[Antenatal Diagnosis](#)

[Unresolved questions](#)

[References](#)

Abstract

Autosomal recessive "malignant" osteopetrosis is a rare congenital disorder of bone resorption (less than 1:200,000 births). It is caused by the failure of osteoclasts to resorb immature bone. This leads to abnormal bone marrow cavity formation and clinically to the signs and symptoms of bone marrow failure. Impaired bone remodeling causes bony narrowing of the cranial nerve foramina, which results in cranial nerve, especially optic nerve, compression. Pathologically there is a persistence of the primary spongiosa characterized by cores of calcified cartilage within bone. Abnormal remodeling of primary, woven bone to lamellar bone results in "brittle" bone that is prone to fracture. Thus fractures, visual impairment, and bone marrow failure are the classical feature of the disease. Osteopetrosis has been reported in most ethnic groups, although, as the disease is very rare, it is more frequently seen in ethnic groups where consanguinity is common. Infantile onset osteopetrosis should also be distinguished from the much milder autosomal dominant adult disease and the carbonic anhydrase II deficiency syndrome, which is associated with renal tubular acidosis and less severe osteopetrosis. The disease is heterogeneous, and while up to 50% of cases are likely to be due to mutations in the ATP6i gene, a number of genetic etiologies are likely.

Keywords

Osteopetrosis, osteoclasts, anemia, optic nerve compression, bone marrow transplant, ATP6i.

Disease name / synonyms

- Osteopetrosis,
- Infantile osteopetrosis,
- Malignant osteopetrosis,
- Autosomal recessive osteopetrosis,
- Brittle bone disease,
- Marble bone disease,
- Albers-Schonber disease.

Excluded Diseases

- Autosomal dominant osteopetrosis,
- Osteopetrosis with renal tubular acidosis,
- Carbonic anhydrase II deficiency,
- pycnodysostosis

Diagnosis criteria /definition

Autosomal recessive "malignant" osteopetrosis is a rare congenital disorder of bone resorption. It is caused by the failure of osteoclasts to resorb immature bone [1-3]. Most patients present in the first year of life. Presenting features are variable (see below). Key features are radiologically dense (sclerotic) bone changes, bone fractures, visual impairment due to optic nerve encroachment, anemia and compensatory hepatosplenomegaly due to bone marrow failure. Diagnosis can be confirmed by bone biopsy. A molecular diagnosis is also possible (see etiology).

Differential diagnosis

The phenotype is so characteristic that if the key features are present in infancy or early childhood the diagnosis is usually secure. A bone biopsy will confirm this and may help further classify the condition. Isolated sclerotic bones in late childhood or adulthood are not likely to be due to autosomal recessive osteopetrosis.

Incidence

Very rare in most populations (less than 1:200,000 births). More common in Costa Rica and probably Pakistan/India. Much more common in consanguineous populations.

Clinical Description

Affected children usually present within the first year of life and frequently within the first three months [4, 7-9]. Parental concern regarding the child's vision is the most common presenting complaint. Failure to achieve normal visual milestones, roving eye movements, and/or squint are often reported. Other presentations include failure to thrive and recurrent infection, both secondary to the underlying anemia and bone marrow involvement. Hypocalcemic seizures, excessive bruising, fractures, nasal congestion, and an abnormal craniofacial appearance are less common presenting complaints [4, 7-9]. These symptoms are non-specific and while hepatosplenomegaly is invariably present at an early age this may be missed and because of the disease rarity a correct clinical diagnosis is often not initially made. Frequently it is the distinctive sclerotic bony changes seen on a serendipitously performed X ray that alerts the clinician. If radiological appearances are supportive and the child has features of anemia with compensatory erythropoietic hepatosplenomegaly and/or visual impairment then the diagnosis is highly likely. A skeletal survey should be performed and reviewed by an experienced pediatric radiologist to confirm the diagnosis. There are a large number of individually rare genetic conditions associated with osteosclerosis or osteopetrosis.

Only a small number of these are associated with anemia and visual impairment [10]. Dysosteosclerosis is a very rare condition which can present with a very similar phenotype to osteopetrosis. These patients are not usually anemic however and while the initial X ray changes may be indistinguishable from osteopetrosis they later develop the characteristic irregularly coarse submetaphyseal trabecular pattern [11-12].

A bone biopsy is not usually required for diagnostic purposes, although it may prove beneficial when the initial diagnosis is unclear or the child's clinical progress varies significantly from the established phenotype. It may also be helpful in further classify the genetic etiology of the condition and thus aid in a molecular diagnosis (see below-Etiology).

Management including treatment

Initial management should focus on establishing the severity and extent of the disease.

Hematology

The majority of patients, because of a failure of bone marrow development, are anemic and many become transfusion-dependent. Transfusion dependency prior to 3 months of age is a sign of severe disease and thus a poor prognostic sign [4,9,13]. These children often have massive compensatory extramedullary hemopoietic hepatosplenomegaly. While most transfusion-dependent patients remain so, some acquire hemopoietic competence, probably as a result of extramedullary recruitment or perhaps bone marrow recrudescence [9]. Because of the possibility of future bone marrow transplantation, blood should ideally be taken for tissue typing prior to the initial transfusion.

Recurrent infection

The generation of superoxide by peripheral blood leucocytes is defective in patients with osteopetrosis [14 15]. This, along with the anemia, poor nutrition, recurrent hospital admissions, and the frequent ear, nose, and throat complications, results in a greatly increased susceptibility to infections. This can be especially debilitating in the young child. The infections are usually of viral etiology, most commonly affect the respiratory tract, and are often prolonged. Infections, especially pneumonia and septicemia, are a common cause of death [4, 7-9, 13]. In infancy this infection risk should be viewed as an indication for bone marrow transplantation (BMT).

Vision

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 pediatric 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 electroretinogram may help rule out associated neurological disease [16]. The visual loss, caused by bony encroachment of the optic nerve at the level optic foramina, is progressive and almost always occurs within the first year of life [4, 9, 13, 16]. Severely affected children may show absent or severely attenuated VEPs within the first three months, and in some this is apparent at birth. Because the rate of visual deterioration tends to plateau after 18 months to two years, some children, despite poor early neurophysiological findings, maintain a degree of visual acuity into later childhood.

Unfortunately an improvement in visual status is unlikely, despite treatment [9, 13, 16]. Optic nerve decompression is a hazardous procedure and reports suggest success only in mildly affected older children [4, 17, 18]. With younger children the focus should be on obtaining a BMT, with the expectation being the preservation of existing sight rather than a reversal of the disease process. Children with intact vision must be regarded as urgent priority in regard to BMT waiting lists.

Hearing

Hearing is less commonly affected than vision, with approximately a third of patients having some degree of hearing loss [4 7-9 19]. The impairment usually manifests within the first year of life. The pathology of the deafness is unclear but is probably secondary to a combination of bony compression of the nerve, sclerosis of the middle ear ossicles, and/or chronic middle ear effusion. Early insertion of ventilatory "grommet" tubes should be considered.

Failure to thrive

Failure to thrive is seen in many osteopetrotic children and is a result of the chronic anemia, feeding problems caused by bulbar nerve involvement, nasal congestion, and recurrent infections [4, 9, 19, 20]. Many children require nasal gastric feeds to improve energy intake. This procedure may be difficult as osteopetrotic children often have choanal narrowing, nasal congestion, and obstructive sleep apnea, and will not tolerate nasogastric tubes [19]. The alternative of a gastrostomy carries the risk of infection in those patients who may be candidates for BMT.

Other neurological disorders

As well as II and VIII, other cranial nerves may be involved in osteopetrosis. This is again a result of bony encroachment, but the

manifestations are usually relatively mild and thus less obvious [9, 21, 22]. Children may have some paucity of facial expression or difficulties with feeding and swallowing. Less commonly there is neurophysiological evidence of involvement of the peripheral motor nerves, probably caused by bony pressure at the nerve root [9].

Children with osteopetrosis have multiple handicaps and thus an accurate assessment of their cognitive function is difficult. Developmental delay, if present, is usually consistent with the extent of physical and visual impairment, and the severity of chronic illness the child has suffered [13, 23].

Children with classical congenital osteopetrosis should not have central nervous system involvement. Significant developmental delay or regression, unexplained seizures, retinopathy, or radiological brain changes should alert the clinician to the rare, but well reported, neurodegenerative condition that can affect patients [4, 9, 24-27]. This association between osteopetrosis and neurodegeneration probably encompasses a heterogeneous group of diseases. They are often rapidly progressive and as they generally carry a poor prognosis the finding of CNS involvement may constitute a contraindication to BMT. It is thus mandatory to perform a thorough clinical, radiological (magnetic resonance imaging of the brain), and neurophysiological examination on all osteopetrotic patients.

Cardiac disorders

While not reported in the literature, we know of four patients who had acute pulmonary hypertension and whom have subsequently died. Another had pulmonary valve stenosis and regurgitation with post-valvular pulmonary dilatation. It would seem prudent therefore to perform a cardiac assessment in all patients.

Biochemistry

Complications of hypocalcemia (especially pre-BMT) and hypercalcemia (post-BMT) are common. Both can be difficult to control. The vitamin D analogues and calcium supplements used to treat the former may make the latter more likely post-BMT and the clinician should be careful not to "over treat" [9]. Bisphosphonates, phosphate infusions, and calcitonin may be useful in the severe recalcitrant hypercalcemia sometimes seen post-transplantation [28].

Orthopedic disorders

Fractures are common and are one of the classical features of osteopetrosis. The susceptibility is variable and in some children recurrent fractures are the most debilitating part of the disease [4 7-9 13]. They tend to occur only

after moderate trauma and are thus rare in infancy. The long bones are most frequently affected [29 30]. Patients seem to be susceptible to fractures for some time after successful BMT. Most fractures can be treated with conservative closed techniques and in most cases the fracture heals normally but with some delay. Open treatment with fixation can be technically demanding because of the sclerotic bone. In particular intermedullary rod fixation of femur fractures is extremely difficult because of the bony obliteration of the normal marrow cavity. Problems with bleeding and infections are frequently encountered because of the underlying disease [29, 30]. Because of these problems and the overall prevalence of fractures, optimal pain management is essential in the management of affected children.

Children with osteopetrosis often have an abnormal head shape. Macrocephaly and frontal bossing are common, especially in early childhood [31, 32] Craniosynostosis may be a problem in both the transplanted and non-transplanted patient. Regular measurement of head circumference and a computed tomography scan with surgical referral if necessary is suggested. Surgical vault release however may result in significant intracranial perioperative bleeding, probably secondary to underlying cerebral venous obstruction at the level of the exit foramina [9].

Children frequently have dental problems; failure of tooth eruption, recurrent caries, and abnormal dentinogenesis have all been reported [7-9 33].

Medical treatment

Corticosteroids, high dose calcitriol, and interferon gamma have all been reported to be helpful in the treatment of osteopetrosis [34-38]. The initial promise of steroids and calcitriol has proved unwarranted although there may be some initial short term benefit [38, 39]. Key *et al* reported very encouraging results with recombinant human interferon gamma -1b (1.5 µg/kg, three times per week) [38]. Increased bone resorption and haematopoiesis and improved leucocyte function was seen in the small number of patients studied. The study group however had a mean age of 4 years and thus they were in a relatively stable period of the disease. Most importantly there was no control group and follow up was for only 18 months. More studies of interferon are warranted and awaited. Our experience with the drug in the early onset severely affected group of patients is disappointing, although in the older infant it may help reduce infection and improve bone resorption.

Palliative care

In some patients, because of the severity of their disease, aggressive treatment is not warranted and palliative care is indicated. Adequate pain relief is essential and the assistance of the local palliative care team and support services should be sought.

Outcome

Natural history

Osteopetrosis has a high mortality rate in the first two years of life. Children with severe disease, that is, those with significant visual and hematological impairment before the age of 3 months, frequently die in infancy [4, 7-9, 13]. The cause of death is often bone marrow failure and overwhelming infection. It is unlikely that medical therapy significantly alters the natural history of the disease in this group of patients and urgent BMT should be sought. Conversely, children who are not transfusion-dependent and are alive at 2 years form a relatively favorable prognostic group. While orthopedic complications continue to be a problem and there is usually significant visual impairment, the mortality rate is low and, in the absence of a suitable bone marrow donor, treatment with interferon gamma or high dose calcitriol may be warranted. Further studies of the long term prognosis in this group of children are needed. Reports of adults with autosomal recessive osteopetrosis are rare.

Bone marrow transplantation

BMT is the only treatment that has been proven to significantly alter the course of disease. While successful recipients may continue to have minor orthopedic and dental problems and their vision rarely significantly improves, their hemopoietic 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 in 19 patients with a HLA identical sibling donor. Recipients of non-genotypically identical grafts had significantly worse results with only a 13% five year disease free survival in those receiving marrow from an HLA haplotype mismatched related donor [13]. Transplantation success rates are now much higher however and haploidentical donors may be appropriate in the right clinical setting. Bone marrow immunoscintigraphy, by showing the extent of marrow recrudescence, may be useful in monitoring the effectiveness of therapy after transplantation [40].

Children with osteopetrosis require a multidisciplinary approach. As well as the pediatrician, a feeding specialist, ophthalmologist, audiologist, dentist, and the

bone marrow transplant team should be involved. Initial management should focus on establishing the severity of the illness with emphasis on the neurological, hematological, and feeding status of the child. Tissue typing should be arranged and based on the availability of a suitable donor BMT performed as soon as it is practical. Urgent status should be reserved for those children with intact vision and those with severe disease. Whether or not a BMT is performed, continuing management should focus on meeting the child's educational, social, and medical needs.

Etiology

Autosomal recessive osteopetrosis is a disorder of osteoclasts. Osteoclasts are responsible for the resorption and thus remodeling of bone. Osteopetrosis is likely to be caused by a number of genetic causes. Mutations in the gene *ATP6i* (TCIRG1) coding for an osteoclast specific $\alpha 3$ subunit V-ATPase vacuolar pump have been found in a approximately 50% of affected children [41]. This protein is responsible for creating the highly acidic microenvironment underneath the osteoclasts-resorbing lacuna required for the solubilization of the hydroxyapatite crystals of bone. Recently mutations in the *C1C7* (*Clcn7*) chloride channel have been found to also cause infantile recessive osteopetrosis. This gene can cause a more mildly disease in an autosomal dominant fashion. Other genetic etiologies are likely to be discovered in the near future. ATP6i and C1C7 both affect osteoclasts resorption. These patients bone biopsies reveal normal or increased numbers of osteoclasts, whereas a few patients have osteoclast depleted biopsies and may have defects in osteoclasts differentiation.

Genetics Counseling

Infantile osteopetrosis is an heterogeneous disease and a number of genetic loci are likely. All cases are likely to be inherited in an autosomal recessive fashion. Thus there is a 1 in 4 (25%) risk of having another affected child with each subsequent pregnancy. Molecular analysis is available.

Antenatal Diagnosis

A radiological diagnosis is possible in the third trimester. Molecular diagnosis is possible much early (CVS 11-13 weeks), providing that a genetic etiology has been found in the proband [42].

Unresolved questions

What are the other genetic causes?
 What is the role of optic foramin decompression?
 What is the role of interferon and steroids in the management?

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