A Guide to Osteopetrosis for Patients and Families

A publication of
The OsteoPETrosis Society

The Osteopetrosis Society is designated as a 501c3 non profit organization by the Internal Revenue Service (IRS)
A Guide to Osteopetrosis for Patients and Families

Presentation

Osteopetrosis presents in a variety of different ways, each having to do with a central problem in the bone. It may be known by various other names such as Albers-Schoenberg disease, and “marble bone disease”. Osteopetrosis is typically divided into three categories: autosomal recessive osteopetrosis, intermediate autosomal osteopetrosis, and autosomal dominant osteopetrosis.

Autosomal recessive osteopetrosis (ARO) presents in infancy and can cause severe problems such as low red blood cell counts (anemia), low platelet counts (thrombocytopenia), and low white blood cell counts (leukopenia), which can predispose to serious infections. It can sometimes present at first with seemingly mild findings such as chronic nasal stuffiness. Patients often also suffer from fractures and slow growth. Vision loss can occur due to compression of the optic nerves by growing bone. Patients frequently have low calcium levels in their blood.

Intermediate autosomal osteopetrosis (IAO) typically presents in childhood. Patients have very dense bones which tend to fracture easily. Patients can have visual impairment, and can also have anemia, which is often not as severe as the infantile form of the disease. Patients also can have severe dental problems including teeth which are slow to come in, poor formation of the enamel, and chronic infections of the jaw (osteomyelitis) and other bones.

Autosomal dominant osteopetrosis (ADO) can be present at any time from childhood on. It is sometimes referred to as the benign form of the disorder, but still can cause significant problems for patients. They still have dense bones which are prone to fracture with little trauma. Patients also can suffer from scoliosis, early arthritis, and can have infections of the jaw and other bones.
Diagnosis

The diagnosis of osteopetrosis starts with clinical suspicion of the condition. This can be problematic, as many clinicians are unfamiliar with this condition and how it is diagnosed. In all of us, bone is continually being formed and broken down. This is done to repair damage and keep bone healthy. Keeping healthy bone requires a balance between cells that build bone (osteoblasts) and cells with break down bone (osteoclasts). The main problem in osteopetrosis is that osteoclasts don’t work well, whether because they lack ability to break down bone or because they aren’t present.

If a person is suspected of having a bone disorder, their health care provider may order routine blood tests. These tests may be normal. However, it is common for the level of calcium in the blood to be low, which can lead to muscle problems and seizures. Clinicians may find that the parathyroid hormone level, which helps keep the calcium level in the blood stable, is elevated in osteopetrosis. Patients with more severe forms of osteopetrosis also have low red blood cell counts (anemia) and low platelet counts (thrombocytopenia).

Clinicians who suspect that a patient may have osteopetrosis may order more specific blood tests such as tartrate-resistant acid phosphatase (TRAP) and the BB isoenzyme of creatine kinase (CK-BB). These can be elevated in types of osteopetrosis where the osteoclasts are present, but function poorly.

X-rays are crucial in the diagnosis of osteopetrosis, with patients having bones which appear very thick and bright, indicating increased bone density (osteosclerosis). In particular, the skull is usually very thick and dense. Likewise, the vertebrae are dense. Some bones may show a “bone-in-bone” appearance. Bone biopsy is not always performed, but if done will show either poorly functional osteoclasts or greatly reduced number of osteoclasts.

Genetics

The genetics of osteopetrosis is quite complex, with changes to at least eight genes known to cause osteopetrosis. Gene mutations can be grouped into those
which cause osteoclasts to lose the ability to break down bone (osteoclast-rich), and those where the osteoclasts are not present (osteoclast-poor). Some patients with osteopetrosis have a recessive form of the disease, meaning that both copies of a gene are not working, while others have a dominant form of the disease, meaning that only one copy of a gene is not working. Some patients with a mutation in a gene known to cause osteopetrosis never develop symptoms of the disease. Genetic testing is available clinically from several laboratories in the United States.

**Management**

In patients with severe forms of osteopetrosis, it may not be possible to manage the disease with medications or conventional therapies. In those patients, transplantation of blood stem cells from someone without osteopetrosis can provide functioning osteoclasts, as these cells come from the blood. Patients receive these blood stem cells by infusion and they generally go to the bone marrow, and start to grow. As the bone marrow is abnormal in osteopetrosis, getting the donor cells to "take" is sometimes harder than for other diseases.

Patients have to be prepared for transplant prior to providing the donor blood stem cells. Chemotherapy and/or radiation are required so that the donor cells are not rejected. During this period of time, patients have a high risk of infections. Osteopetrosis patients are also at risk for other complications with transplant, such as liver or lung disease, or high calcium levels after transplant. Some of these transplanted-related complications can be life-threatening. Unfortunately, some patients do not survive the transplant process. Even under the best of circumstances, transplantation is a major medical procedure with a significant recovery period. Due to these risks, it is generally only used in cases of severe osteopetrosis, particularly the infantile form of the disease.

When the transplant is successful, patients can experience significant improvement in their health. Over time the new osteoclasts can help to remodel the bone, making it virtually normal in appearance; on this basis, transplantation can be considered the definitive treatment for osteopetrosis. Unfortunately, transplantation
cannot fix issues that have occurred prior to transplant, such as blindness.

Not every patient requires a transplant for osteopetrosis. Many patients require medical management for their condition. This includes supplementation, certain vitamins, and medication.

Calcium supplementation (for example, Tums® or other supplements) is sometimes needed to treat low levels of calcium in the blood. The human body requires a steady level of calcium in the blood to work properly. Low levels of calcium in the blood are due to the inability of osteoclasts to release calcium from the bones.

Calcitriol (Rocaltrol) is the “active” form of vitamin D that helps the body absorb calcium from the gut and release calcium from the bones. Calcitriol is sometimes needed to treat low levels of calcium in the blood in addition to calcium supplementation.

Interferon gamma-1b (Actimmune®) is a medicine that was approved by the U.S. Food and Drug Administration (FDA) in 1999. Actimmune® is indicated for delaying time to disease progression in patients with severe, malignant osteopetrosis. Published data show beneficial effects in individuals with osteopetrosis such as decreasing bone density, increasing hemoglobin, and decreasing the risk of infection. More information is needed to better determine the role of interferon gamma-1b in the medical treatment of patients with osteopetrosis.

A number of specialists may be required to treat patients with osteopetrosis. Medical management aside from transplant is frequently done by an endocrinologist who is comfortable with metabolic bone disease. Patients with osteopetrosis who have scoliosis should follow with a spine specialist who is familiar with osteopetrosis. An orthopedic surgeon who is familiar with osteopetrosis should be sought to treat for fractures and other problems with the bones and joints that may arise. Bone and joint problems may require surgical management or may be amenable to nonsurgical management such as physical therapy.

Patients with osteopetrosis should be followed for vision changes or vision loss, which involves both imaging of the optic canal and clinical examination, ideally performed by a neuro-ophthalmologist. Hydrocephalus (water on the brain) is a risk
for patients with autosomal recessive osteopetrosis and should be followed both clinically and with imaging.

Complications

One of the most difficult concepts for both patients and physicians who study osteopetrosis to understand is the tremendous variability in disease severity among people with the same mutations, even within the same family. For example, someone with severe disease can have a child who is a non-penetrant carrier (i.e. has the disease causing mutation, but doesn’t have the disease) or someone with very mild disease can have a child with severe disease. No one understands why there is such variability in disease severity, but it is something that has been observed by physicians who take care of families with this condition.

Fractures are the most common complication of osteopetrosis. However, the number of fractures per patient is highly variable. Some people only have a few fractures and others can have over 100 fractures. Many fractures occur without significant trauma and sometimes they don’t heal (nonunion). Additionally, if the fracture requires surgery the bone is often difficult to operate on because it is both very hard and brittle. This is the reason why osteopetrosis is often referred to as “marble bone disease”.

Osteonecrosis (death of bone tissue) generally presents as a non-healing piece of bone, most typically in the jaw or upper mouth. Osteonecrosis occurs in 11-16% of adult patients. The dead bone frequently becomes infected and can be very difficult to treat. Osteonecrosis often looks like a non-healing sore in the mouth with exposed bone. Sometimes it can occur after a dental extraction.

Visual loss (blindness and other less severe visual problems) is more common with severe recessive forms of osteopetrosis. Visual loss can occur when the optic nerve grows, but the hole in the skull (called a foramen) doesn’t get bigger and traps the nerve, choking it off. Rates of blindness vary from study to study with a range of 5-19%. Blindness can be prevented by following a patient carefully and promptly referring the child to a neurosurgeon, who can operate to relieve this
problem, if necessary.

Bone marrow failure generally only occurs in the most severely affected patients, such as in infantile recessive osteopetrosis. In these patients bone replaces bone marrow (blood cells are made in bone marrow) and can cause them to become anemic. In contrast, this complication only occurs in <3% of dominant osteopetrosis patients.

The Osteopetrosis Society was organized to increase awareness, educate patients and providers and expand research. The Society’s goal is to improve treatment, find a cure for the disease, and advocate for patients and families who are affected.