Richard M. Pauli, M.D., Ph.D.
Midwest Regional Bone Dysplasia Clinics
revised 9/2009

OSTEOPETROSIS
NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Osteopetrosis is neither exhaustive nor cited. It is based upon the available literature as well as personal experience in the Midwest Regional Bone Dysplasia Clinics (MRBDC). It is meant to provide a guideline for the kinds of problems that may arise in individuals with this disorder, and particularly to help clinicians caring for a recently diagnosed person. For specific questions or more detailed discussions, feel free to contact MRBDC at the University of Wisconsin – Madison [phone – 608 262 6228; fax – 608 263 3496; email modaff@waisman.wisc.edu].

Osteopetrosis means 'marble' or 'rock-like' bone. That term is a descriptive one and does not define a specific process. The Osteopetroses are a subclass of sclerosing bone disorders. In turn, there are a number of kinds of Osteopetrosis, ranging from exceedingly severe autosomal recessive forms that lead to death secondary to bone marrow failure to far milder autosomal dominant types. This summary only deals with these dominant forms. These are sometimes termed Albers-Schonberg disease.

Dominant Osteopetrosis affects between 1/20,000 and 1/100,000 individuals. There is remarkable variability of severity and incomplete penetrance (i.e. some individuals with the genetic abnormality show no manifestations). Around 90% of those with one of the gene mutations have radiologic penetrance, but only 65% to 80% show clinical penetrance.

Both radiologically and at a molecular level there are two main types of dominant Osteopetrosis. Type I has marked generalized skull involvement, no spine involvement, and generalized long bone involvement. Type II has sclerosis only of the skull base, the spine shows bone-in-bone changes or so-called rugger jersey feature (striped vertebrae), there is considerable pelvic sclerosis and long bone involvement is quite variable. In both types there is an imbalance of osteoclast and osteoblast function, In Type II this clearly arises from abnormally low osteoclast function.

MEDICAL ISSUES TO BE ANTICIPATED

PROBLEM: **BONE FRAGILITY**
EXPECTATIONS: Although bone is more dense, there is excess fragility (similar to chalk) and increased risk for fractures. Curiously, this seems to be so only in type II and not in type I. In type II the risk of fracture is 70-85% and total lifetime fracture number ranges from 0 to 40, with a median of around 3. The femur seems to be particularly susceptible with nearly ½ of individuals experiencing at least one femoral fractures and 1/3 of all fractures being of the femurs. There also seems to be increased frequency of delayed union, non-union and other complications following fracture treatment.
MONITORING: No monitoring is needed, but a high level of suspicion that fracture may occur after modest trauma should be maintained.
INTERVENTION: There should be modest limitations of activities that might result in marked trauma such as collision sports. Fracture treatment is as in other individuals, but it may be appropriate to immobilize somewhat longer than average after fractures.

PROBLEM: **DENTAL ABNORMALITIES**
EXPECTATIONS: Most have more than average caries. Dental abscesses are quite common – arising in around 10-15%. Mandibular and maxillary osteomyelitis develops in 10-15%, too, probably because of decreased vascularity. Osteomyelitis is mostly a problem of older adults.
MONITORING: Compulsive dental care and follow-up should begin in early childhood and continue throughout life.
INTERVENTION: When complications arise, they are treated as in other individuals.

PROBLEM: **OSTEOARTHRITIS**
EXPECTATIONS: This often arises prematurely in middle adulthood. It probably affects around 25% of those with Osteopetrosis and most commonly affects the hips. Often hip arthritis is sufficiently severe to require hip replacement surgery. The mechanism for this increased incidence of osteoarthritis is unclear.
MONITORING: Periodic query regarding joint pain and limitations of activity or function.
INTERVENTION: Modest limitation of repetitive weight bearing may delay onset of osteoarthritis. Likewise, avoidance of activities with a high risk for severe joint injury should be encouraged. Although controversial, glucosamine (in adults) may have some benefit in slowing or reversing arthritic changes.

PROBLEM: **LUMBAR SPINE PAIN**
EXPECTATIONS: Chronic lumbar pain occurs in 25% of affected adults. Mechanism of its development is not known. Sometimes pain may be secondary to compression fractures.
MONITORING: Periodic query regarding lumbar pain and reassurance that it does not likely indicate another, independent problem.
INTERVENTION: Routine pain management is appropriate.

PROBLEM: **SCOLIOSIS**
EXPECTATIONS: Scoliosis arises in about 25% of affected individuals. Usually it develops in adolescence and seems quite similar to idiopathic scoliosis. It is usually not severe.
MONITORING: Clinical monitoring yearly from mid-childhood until completion of growth. If a worrisome curve seems to be developing then radiologic assessment should be done.
INTERVENTION: Most often no treatment is needed. If more than a mild curve arises, then standard treatments (i.e. bracing, surgery) are indicated.

PROBLEM: **COXA VARA**
EXPECTATIONS: Arises in around 10% of individuals. Nearly always it is insufficiently severe to require intervention.
MONITORING: -
INTERVENTION: -

PROBLEM: **BOWING OF LONG BONES**
EXPECTATIONS: This is uncommon. When it does arise, it is usually of the femora or tibiae.
MONITORING: Periodic clinical assessment of leg alignment.
INTERVENTION: In a few individuals surgical realignment will be needed; however, surgery should be reserved for those who must have it because of risks of delayed union or non-union.

PROBLEM: **CRANIAL NERVE COMPRESSION: VIII**
EXPECTATIONS: All cranial nerve compressions are uncommon, in sum affecting less than 5% of individuals (but see below). Hearing loss secondary to compression of the VIII cranial nerve is the most common complication, and seems to be much more common in Type I than in Type II
MONITORING: Audiometric evaluation every 2-3 years in those with Type I.
INTERVENTION: Treatment is difficult. Hearing aids may be of some benefit.

PROBLEM: **CRANIAL NERVE COMPRESSION: OPTIC ATROPHY**
EXPECTATIONS: Most studies suggest that only around 1% of affected individuals develop visual changes from optic atrophy arising secondary to skull base compression. However, one recent study showed that nearly 20% of adults had some such changes.
MONITORING: Ophthalmologic assessment every 2-3 years.
INTERVENTION: -

PROBLEM: **CRANIAL NERVE COMPRESSION: VII**
EXPECTATIONS: Facial paralysis arises rarely.
MONITORING: -
INTERVENTION: -

PROBLEM: **CERVICAL CORD COMPRESSION**
EXPECTATIONS: Very rarely high cervical myelopathy develops.
MONITORING: Screening neurologic assessment every 2-3 years and whenever any relevant symptoms arise.
INTERVENTION: Decompression surgery is indicated in those rare individuals in whom this develops.

PROBLEM: **BONE MARROW FAILURE**
EXPECTATIONS: Although common in autosomal recessive Osteopetrosis, this is very rare in those with dominant forms, affecting between 1% and 3%.
MONITORING: CBC, differential and platelet count every 2-3 years.
INTERVENTION: Referral to a hematologist should abnormalities be demonstrate by such screening.

GENETICS AND MOLECULAR BIOLOGY

These forms of Osteopetrosis are autosomal dominant processes. This means that if an individual is identified as affected, it is likely that one or the other of their biologic parents also have the abnormal gene (even if they are unaware of it). Lateral skull, pelvis and lateral spine radiographs are usually sufficient to ascertain if a parent has osteopetrotic changes. Even if no changes are found it is still possible that one or the other parent carries the abnormality silently. In those who are affected (or who carry the gene abnormality silently) there will be a 50% risk for each child to inherit the abnormally functional gene copy and around a 35% chance that they will be clinically affected.

The genes causing both Type I and Type II have been identified. Type I results from changes in *LRP5* (low density lipoprotein receptor 5), abnormalities of which also can result in other increased bone density disorders. Type II arises from mutations in *CLCN7* that codes for a chloride channel protein. There may be yet undiscovered causes of Type II since only around 75% of affected individuals have a demonstrable mutation in *CLCN7*. Recently evidence has been found for CLCN7 also causing an intermediately severe form of Osteopetrosis (more severe than the typical dominant form but not as severe as the recessive form). Some families who have had one child with typical dominant Osteopetrosis may be at risk to have an affected child with this intermediate form.