Osteogenisis imperfecta

Osteogenisis imperfecta (OI) is " a rare genetic disorder of collagen synthesis associated with broad spectrum of musculoskeletal problems, most notably bowing and fractures of the extremities, muscle weakness, ligamentous laxity, and spinal deformities."

(Binder, 386). Other collagen-containing extraskeletal tissues, such as the sclerae, the teeth, and the heart valves are also affected to a variable degree. OI has a " common feature of bony fragility associated with defective formation of collagen by osteoblasts and fibroblasts." (Smith, 1983, 13) This disease, involving defective development of the connective tissues, is usually the result of the autosomal dominant gene, but can also be the result of the autosomal recessive gene. Spontaneous mutations are common and the clinical presentation of the disease remains to be quite broad. (Binder, 386)

OI is most commonly referred to as " brittle bones", but other names include: fragilitas ossium, hypolasia of the mesenchyme, and osteopsathyrosis. Osteogenisis imperfecta is still not completely understood, and while there have been advances in diagnosing the disease, treatment is still limited.

Osteogenisis imperfecta is the result of mutations in the genes for type I collagen.

In the mild dominantly inherited form of OI (type I), " a non-functional allele for the alpha 1 (I) chain halves collagen synthesis," (Smith, 1995, 169) and is largely responsible for the inheritance. Single base mutations in the codon for glycine causes lethal (type II) OI by wrecking the formation of the collagen triple helix. Types III and IV are the " less dram- atic outcomes of

similar glycine mutations in either the alpha 1 (I) or the alpha 2(I) chains. (Smith, 1995, 169)

The clinical signs can be caused from defective osteoblastic activity and defective mesenchymal collagen (embryonic connective tissue) and its derivatives, such as sclera, bones, and ligaments. The reticulum fails to differentiate into mature collagen or the collagen develops abnormally. This causes immature and coarse bone formation and thinning. (Loeb, 755)

The signs and symptoms of OI vary greatly depending on the type. The most commonly used classification is the Sillence (type I to IV):

Type I is the mildest form of OI and is inherited as an autosomal dominant trait. The sclerae(middle coat of eyeball) is distinctly blue. Type I is broken down into IA and IB -- the difference being whether dentinogenesis is present. IA has a life expectancy nearly the same as the general public. The physical activity is limited, and may appear to have no disability at all. The bones have a mottled or wormian appearance, forming small islands. (Isselbacher, 2111)

Type II is lethal in utero or shortly there afterbirth. The survivors live from just a few hours to several months. The kayotypes of parents are usually normal. This type is broken down into three subgroups: IIA is characterized by a broad, crumpled femora and continuos rib beading, IIB by minimal to no rib fractures, and IIC by a thin femora and ribs with extensive fracturing.

While in the uterus, there is poor fetal movement, low fetal weight, poor ossification of the fetal skeleton, hypoplastic lungs, the long bones of the

upper and lower limbs are shortened or deformed, and the head is soft. Intrauterine fractures occur, and parinatal death is usually from intracranial hemorrhage due to vessel fragility or respiratory distress from pulmonary hypoplasia. The bones and other tissues are extremely fragile, and massive injuries occur in utero or delivery. The ribs appear beaded or broken and the long bones crumpled. (Isselbacher, 2111)

Type III and IV are intermediate in severity between types I and II. Type III differs from I in its greater severity, and from IV in that it increases in severity with age. It can be inherited as either a autosomal recessive or dominant trait. The sclerae is only slightly bluish in infancy and white in adulthood, although the average life expectancy is 25 years. Type IV is always dominant. With types III and IV multiple fractures from minor physicalstressoccurs leading to progressive and severe deformities. Kyphoscoliosis may cause respiratory impairment and predisposition to pulmonary infections. " Popcorn-like" deposits of mineral appear on the ends of long bones. (Isselbacher, 2111)

The symptoms of OI tarde (types I, III and IV) can appear when the child begins to walk, and lessens with age. The tendency to fracture decreases and often disappears after puberty. Later in life, particularly during pregnancy and after menopause, more fractures occur. The bones are usually slender with short, thin cortices and trabeculae (fibers of framework), but can also be unusually thin. (Smith, 1983, 136) Narrow diaphysis of the long bones contributes to the fractures and bowing deformities. Scoliosis is common. The haversian cells are poorly developed. The bones lack minerals needed to form bone matrix. Epiphyseal fractures (end of the bone) results in

deformities and stunted growth (dwarfism). Osteopenia, the decrease in bone mass, is symptomatic.

Other signs of OI include hyperextensibility of the joints -- double-jointedness-- and abnormally thin, translucent skin. Discolored (blue-gray or yellow-brown) and malformed teeth which break easily and are cavity prone are found in patients Patients with OI have a triangular-shaped head and face, a bilaterally bulging skull, and prominent eyes with a wide distance between the temporal region. (Loeb, 755)

Hearing loss by the age of 30-40 is the result of the pressure on the auditory nerve because of the deformity of its canal in the skull, and the development of otosclerosis. Recurrent epistaxis (nosebleeds), bruising and edema (especially at the sight of fractures), difficulty tolerating high temperatures and mild hyperpyrexia are other symptoms. Thoracic deformities may impair chest expansion and the ability to effectively breath deeply and cough. (Loeb, 755) Patients are also more susceptible to infection.

In assessing a patient data is needed about the genetic history and birth of the child, as well as a complete development assessment from birth. Vital signs are taken, and periods of increased heart and respiratory rate and elevated body temperature are note-

worthy. Skin should be examined for color, elasticity, translucency, and signs of edema and bruising. A description of position and appearance of a child" s trunk and extremities and facial characteristics should be noted. The height of the child in terms of expected growth, signs of scoliosis or laxity of ligaments, and range of motion of the joints are all important. Sight and

hearing should be tested since there are sensory problems associated with OI. The appearance of the sclerae and tympanic membranes and defects of primary teeth and gums are important. (Jackson, 1699)

X-rays usually reveal a decrease in bone density. " There is no consensus, however, as to whether the diagnosis can be made by microscopy of bone specimens." (Isselbacher, 2112) DNA sequencing and incubating skin fiboblasts are two ways help diagnose OI.

Prenatal ultrasonography is used to detect severely affected fetuses at about 16 weeks of pregnancy. Diagnosis of the lethal type II by ultrasound during the second trimester of pregnancy is by the identification of fractures of the long bones. Compression of the fetal head is seen by ultrasound probe, and low echogeneity of the cranium can be signs of skeletal dysplasia (faulty development of the tissues). Diagnosis is confirmed by postmortem examination including radiography and biochemical studies of cultivated fibroblasts from the fetus. (Berge, 321) Diagnosis by analyzing DNA sequencing can be carried out in chronic villa biopsies at 8-12 weeks.

There is no known treatment of OI at this time. Treatment therefore is predominantly supportive and educational. Because of multiple fractures and bruising, it is important to diagnose this disease in order to prevent accusations ofchild abuse.

Treatment of fractures is often challenging because of abnormal bone structure and laxity of the ligaments. Splinting devices are used to stabilize the bones and to protect against additional fractures. Treatment aims to prevent deformities through use of traction and/or immobilization in order to

aid in normal development and rehabilitation. Limb deformities and repeated fractures can be corrected by intramedullary rods -- telescoping

rods that elongate with growth. After surgical placement of the rods, extensive post- operative care is required because greater amounts of blood and fluid are lost. (Loeb, 755) It should be noted that the healing of fractures appear to be normal. (Isselbacher, 2112) Braces, immobilizing devices and wheelchairs are necessary.

Physical therapy is important in the treatment of OI. Bone fracture density in unfractured bone is decreased when compared with age-matched controls due to limited exercise, so it is essential to stay as active as possible. Physical therapy is also used for strengthening muscle and preventing disuse fractures with exercises with light resistance, such asswimming.

Regular dental visits are necessary to monitor the teeth. Monitoring by opthalmol-

ogists for vision and audiologits for hearing is also essential. Radiologists need to examine the structure and density of the bones, and an orthopedist is needed to set fractures and take care of other bone related problems.

Counseling and emotional support is needed for both the patient and thefamily. It is important not to limit a child because of his/her disabilities, and to realize that many victims of this disease live successful lives. Debrah Morris, a successful business woman, and active fighter for disability rights and helping other patients of OI, says, " If I had the choice to be anyone in the world, I would be exactly who I am. The people I have met, the

challenges I have faced, the opportunities that I have been presented -- all are directly related to dealing with being a little person with brittle bones." (Kasper, 53) Many of the symptoms of OI can be confused with those of a battered child.

X-rays are used to show evidence of old fractures and bone deformities to distinguish the difference. The Osteogenesis Imperfecta Foundation (OIF) has is a national support group that offers assistance to families in this position and to increase public awareness. The OIF has a medical advisory council, chapters, support groups, regional meetings, biennial national conferences, and parent contacts to help families feeling alone and helpless. They also publish a newsletter, provide literature and videos about OI, and sponsors a fund to support research.

Magnesium oxide can be administered to decrease the fracture rate, as well as hyperpyrexia and constipation associated with this condition. (Anderson, 1127) A high-protein, high-carbohydrate, high-vitamin diet is needed to promote healing. A growth hormone has also been administered duringchildhood, and is shown to substantially increase growth. Treatment with bisphosphorates and related agents has been discussed to decrease bone loss, but no controlled studies have been done. (Isselbacher, 2113)

Since there is no cure for oseogenesis imperfecta, appropriate and properly timed rehabilitation intervention is of the utmost importance to ensure that the child is able to function to the best of his/her ability in society. A ten year study that was submitted in 1992 proves this.

25 of 115 children with severe OI were observed since birth or infancy at the National Institutes ofHealth, MD and the Skeletal Dysplasia Clinic at the Children" s National Medical Center in D. C. One was Type I, two Type II, nine Type III, and thirteen Type IV. They were classified by physical characteristics and functional capacity:

Group A consisted of those who were severely dwarfed with large heads and marked bowing , contractures, and weakness of extremities. The highest functional skill expected was independent sitting. Group B was growth deficient, but with a normal sized head. Femoral bowing, scoliosis, and contractures of the hip flexors were characteristics. they were expected to stand and/or ambulate with braces. Group C were less growth deficient, and had good strength, but poor endurance. They had marked joint laxity and poorly aligned lower extremity joints, but were ambulators. (Binder, 386-387)

Group A patients were the most severely involved. Most were basically sitters. The majority were totally dependent in their self care. Group B had the potential to become at least short-distance ambulators. These patients had acquired the ability to move to sitting, but had transitional moving problems, such as sitting to standing. All were part-

ially independent in their self care. Group C had antigravity strength and 50% had good strength in their extremities. All were physically active and age-appropriately independent, but none were good long-distance walkers. (Binder, 387-388)

Progressive rehabilitation of these groups all included posture exercises and active range of motion and strengthing exercises. Group B had additional

ROM and posture exercises, as well as Developmental exercises. Group C added coordination activities.

Conclusion, " Management of patients with OI should address the child" s functional needs. Even though the degree of disability may be severe, management should not be limited to orthopedic procedures and bracing. Treatment planning should be considered, but not totally based on genetic, anatomical, and biochemical abnormalities. Our experi-

ence suggests that clinical grouping based in part on functional potential can be useful in the appropriate management of children with OI."(Binder, 390) Independence was stressed in this study, and even patients with limited sitting ability, upper extremity function can be improved to at least minimal independence in self-help skills. Potential ambulators should be helped because, although their ability might not progress past indoor ambulation, walking will make them more independent and may result in increased bone mineralization.

Poor joint alignment, poor balance, and low endurance can all be improved with persistent, individualized physical and occupational therapy. For best results, therapy should be started as soon after birth as possible. Mainstreaming school aged children is also important. All of this together leads to " age-appropriate social development and markedly improved independence and quality of life in the majority of patients."(Binder, 390)

Osteogenesis imperfecta is the most common genetic disorder of the bone. It occurs in about 1 in 20, 000 live births, and is equally prevalent in all races and both sexes. The Type I OI has a population frequency of about 1 in 30,

000. Type II has a birth incidence of about 1 in 60, 000. Types III and IV are less common and may be as high as 1 in 20, 000. (Isselbacher, 2111) The occurrence of OI in families with no history or blue sclerae is about 1 in 3, 000, 000 births.(Smith, 1995, 171) The recurrence risks in families is estimated to be 6 to 10%, but is only estimated because most couples choose not to have any more children. 15 to 20% of patients with OI do not carry the gene for abnormal collagen, making many wonder if there is yet another genetic problem undiagnosed at this time.(Smith, 1995, 172)