An Introduction to

Osteogenesis Imperfecta

for Medical Professionals, Individuals, and Families

OSTEOGENESIS IMPERFECTA FOUNDATION

A newborn lets out a sharp cry while he is being cleaned and weighed. He screams when he is picked up or when someone touches his leg. An x-ray reveals a fractured femur, as well as several healed rib fractures.

Parents bring their one-year-old daughter to the emergency room. She had been pulling to a stand, when suddenly the parents heard a "pop" and the little girl fell to the floor, crying with the pain of a broken leg. This is the toddler's third fracture since birth.

A teenager checks into the hospital for the second time this year. A few months ago, he had a metal rod put into his tibia. This time, he will undergo risky surgery to put a rod in his spine. Doctors hope that the surgery will halt his progressively worsening scoliosis, which is crowding his lungs and leading to repeated respiratory infections.

At her annual check-up, a 45-year-old woman asks her physician for a referral to a good orthopedist. The woman had several dozen bone fractures in her childhood and teen years. Though she has been fracture-free for a number of years, she is concerned that menopause will weaken her already fragile bones, leading to another cycle of fractures.

The newborn, the toddler, the teenager, and the middle-aged woman all have osteogenesis imperfecta, or "brittle bone disorder." Osteogenesis imperfecta (OI) is a genetic disorder that causes fragile bones as well as other health problems.

This brochure provides the latest information on osteogenesis imperfecta for health care providers and people affected by OI.

For more information on OI, contact the Osteogenesis Imperfecta Foundation at 1-800-981-2663, or visit us on the Internet at www.oif.org.

Myths and Facts About Osteogenesis Imperfecta

Thanks to the work of dedicated researchers and clinicians, we learn more about osteogenesis imperfecta every day. Most babies born today with OI have a good chance of leading independent, successful, and satisfying lives. Traditional treatments are being perfected, and new treatments for strengthening OI bone are on the horizon. Because OI is a rare disorder, many parents who have a child with OI have never heard of it, and their health care providers may never before have treated anyone with OI. This brochure provides families and medical professionals with updated and accurate information.

Myth: A baby with osteogenesis imperfecta should always be carried on a pillow and discouraged from moving.

Fact: Though there are handling techniques and precautions that are useful when caring for an infant with OI, it is in the child's best interest to allow him or her to be held and touched, and to explore independent movement to the greatest extent possible. In fact, immobility increases bone loss and fragility, leading to more fractures.

Myth: You can easily distinguish fractures caused by osteogenesis imperfecta from those caused by child abuse.

Fact: Children with osteogenesis imperfecta can have all types of fractures—spiral, rib, skull, incomplete, displaced, etc. Distinguishing OI from child abuse requires a thorough assessment by a medical professional familiar with OI. Diagnostic tests are also available to help confirm a diagnosis of OI.

Myth: Severe cases of OI are often the result of recessive inheritance.

Fact: In recent years, OI experts have concluded that recessive inheritance of OI is extremely rare.

Most cases of OI are caused by a dominant genetic mutation.

Myth: OI affects only the bones.

Fact: Though fragile bones are the hallmark of OI, people with OI often have other medical problems, including loose joints, early hearing loss, brittle teeth, respiratory problems, and easy bruising.

Myth: OI is a childhood disorder; people grow out of it by their teens.

Fact: OI is a genetic disorder of collagen that is present throughout an affected person's lifetime. Though many people with OI have fewer fractures after puberty, the genetic collagen defect is still present, and fractures and other complications occur throughout the life span.

Myth: Everyone who has OI is shorter than normal, has blue sclera (whites of the eyes), and uses a wheelchair.

Fact: The appearance of people with OI varies considerably. Though many people with OI are short-statured, people with milder forms may be of normal or near-normal height. Some people with OI are born with blue sclera that lighten with age, while others have white sclera from birth. People with OI also have variable mobility, ranging from independent walking to full-time use of a wheelchair.

Myth: Everyone who has OI is diagnosed at birth.

Fact: OI Type I, the most common and mildest form of OI, is rarely diagnosed at birth. Some very mild cases are only diagnosed when a person has a child with OI Type I, and a review of the parent's medical history reveals that he or she has had fractures and exhibited other features of OI.

What is Osteogenesis Imperfecta?

Osteogenesis imperfecta (OI) is a genetic disorder. Most cases involve a defect in type 1 collagen—the protein "scaffolding" of bone and other connective tissues. People with OI have a faulty gene that instructs their bodies to make either *too little* type 1 collagen or *poor quality* type 1 collagen. The result is bones that break easily plus other connective tissue symptoms. OI occurs equally among males and females and it occurs in all racial and ethnic groups.

Several forms of OI have been described, representing wide variation in appearance and severity. Types of OI include mild, moderate and severe forms. Recent research has identified two new moderately severe types that do not appear to have a type 1 collagen defect. It is estimated that approximately 50,000 people in the U.S. have OI.

Below are the clinical features of the major types of OI. **Clinical features vary widely not only between types, but within types, and even within the same family.** Many individuals with OI have only some—not all—of the clinical features. Children with milder OI, in particular, may have few obvious clinical features.

Type I (Mild)

- Most common and mildest type of OI.
- Bones predisposed to fracture. Most fractures occur before puberty.
- Normal or near-normal stature.
- Loose joints and muscle weakness.
- Sclera (whites of the eyes) usually have a blue, purple, or gray tint.
- Triangular face.
- Tendency toward spinal curvature.
- Bone deformity absent or minimal.
- Brittle teeth possible.
- Hearing loss possible, often beginning in early teens.
- Collagen structure is normal, but the amount is less than normal.

Type II (Perinatal Lethal)

- Most severe form.
- Frequently lethal at or shortly after birth, often due to respiratory problems.
- Numerous fractures and severe bone deformity evident at birth.
- Small stature with underdeveloped lungs.
- Collagen is improperly formed.

Type III (Progressive Deforming)

- Progressive bone deformity, often severe.
- Bones fracture easily. Fractures are often present at birth, and x-rays may reveal healed fractures that occurred before birth.
- Short stature.
- Sclera have a blue, purple, or gray tint.
- Loose joints and poor muscle development in arms and legs.
- Barrel-shaped rib cage.
- Triangular face.
- Spinal curvature.
- Respiratory problems possible.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen is improperly formed.

Type IV (Moderate Severe)

- Between Type I and Type III in severity.
- Bones fracture easily, most before puberty.
- Shorter than average stature.
- Sclera are white or near-white (i.e., normal in color).
- Mild to moderate bone deformity.
- Spinal curvature.
- Barrel-shaped rib cage.
- Triangular face.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen is improperly formed.

Types V & VI (Novel Forms)

- Recently identified types of OI.
- At this time no collagen defect has been found.
- Characteristics similar to Type IV OI.
- Additional Type V characteristics include:
  - Dense band adjacent to the growth plate of long bones.

- Development of hypertrophic calluses from fracture or surgery.
- Calcification of the membrane between the radius and the ulna.

- Type VI bones have a "fish scale" appearance under a microscope.

Other features common in people with OI include excessive perspiration, easy bruising, a high-pitched voice, cardiopulmonary abnormalities, loose joints and thin, smooth skin.

How Is OI Inherited?

Researchers now agree that nearly all cases of OI are caused by a dominant genetic mutation. The majority of children with OI inherit the disorder from a parent who has OI. Nevertheless, approximately 35 percent of children with OI are born into families with no history of the disorder. This is usually due to a spontaneous dominant mutation that takes place in the sperm or the egg prior to conception.

When a child with OI is born into a previously unaffected family due to a spontaneous mutation, in most cases the parents have a small increased risk (2-5%) of having another child with OI. Occasionally, a parent may be *mosaic* for a mutation; that is, a mutation that causes OI is present in a percentage of the reproductive cells that give rise to his or her sperm or eggs. In these cases the risk that the parents will have more than one child with OI ranges from 10-50% per pregnancy. Genetic testing can determine whether a parent is a mosaic carrier.

A person with OI has a 50 percent chance of passing on the disorder to each of his or her children. An affected child will have the same mutation, and therefore the same type of OI, as his or her parent. However, the disorder may not affect the child in exactly the same ways it has affected the parent. The child's condition may be more or less severe than the parent.

Unaffected siblings of a child with OI are at no greater risk of having children with OI than the general population.

How is OI Diagnosed?

Bone fractures that occur with little or no trauma are often the first indication that an infant or child may have OI. Babies with Types II, III, and IV are often born with fractures, and/or may show evidence of in utero fractures that have healed. Children with Type I often sustain their first fracture(s) as a result of normal activity during the first several years of life—during a diaper change, while being lifted or burped, or when they begin standing and walking. Some very mild cases of Type I OI are not diagnosed until the teen or adult years.

OI remains primarily a clinical diagnosis. A physician familiar with OI can often diagnose the condition based on the presence of fractures as well as other clinical features. It is important to remember that the presence of clinical features varies widely among individuals. A positive family history for the disorder can help confirm a diagnosis, although spontaneous mutations do occur in previously unaffected families.

There are two types of laboratory tests available to help confirm a diagnosis of OI. These tests are meant to be used in conjunction with a clinical evaluation. A skin biopsy can be analyzed to determine if the quantity or quality of type 1 collagen is abnormal. This approach identifies almost 90% of persons known to have OI. A DNA test can be done on a blood sample to try to locate the mutation that caused OI. Several hundred mutations have been identified. This test identifies about 90% of people with OI. A few individuals test positive for OI on one test and not the other. Approximately 10 percent of individuals with mild OI test *negative* for OI through collagen or DNA testing, despite having the disorder.

OI can be prenatally diagnosed in some cases. Ultrasound can often detect bowing, fractures, shortening or other bone abnormalities, particularly in the more severe forms of OI. Type II OI is identifiable by 14 to 16 weeks gestation, and Type III OI by 16 to 18 weeks gestation. Even when ultrasound is done by a highly qualified technician

or physician, it may not be possible to pinpoint the type of OI (e.g., Type II vs. Type III). Cells obtained through chorionic villus sampling (CVS) can be analyzed for abnormal collagen as well as for a genetic mutation, while cells obtained through amniocentesis can be analyzed for a genetic mutation. OI is caused by many different genetic mutations; therefore, prenatal genetic testing is generally most useful when the mutation of an affected family member is already known.

How is OI Treated?

There is no cure for OI. Currently, OI is treated primarily by managing fractures and active physical rehabilitation to promote as much mobility and independence as possible. Prolonged immobility can further weaken bones and lead to muscle loss, weakness, and more fractures. Many orthopedists prefer to treat fractures with short-term immobilization in lightweight casts, splints, or braces to allow some movement as soon as possible after the fracture.

Physical Therapy and Exercise. Physical therapy should begin as soon as it is evident that an infant has muscle weakness or motor skill delay when compared with same-age peers. It should continue until a child reachs appropriate physical therapy goals. The long-term goal for children with OI is independence in all life functions (e.g., self-care, locomotion, recreation, social interaction, and education), with adaptive devices as needed. Occupational therapy can help with fine motor skills and adaptive equipment for daily living. As a child with OI grows older and gains more independence, he or she will benefit from continued physical activity, such as adapted physical education. Adults with OI also benefit from safe, regular exercise to maintain bone and muscle mass. Swimming and water therapy are particularly well-suited for people with OI of all ages, as they allow independent movement with little fracture risk. Walking is also excellent exercise for those who are able (with or without mobility aids).

Surgery. Many children with OI undergo a surgical procedure known as rodding, in which metal rods are inserted into the long bones to control fractures and improve deformities that interfere with function. There are two basic types of rods. Nonexpandable rods are more versatile but often must be replaced as the child grows. Expandable rods can grow with the bone, but are only appropriate for larger bones (such as the femur) due to their thickness and need to be firmly anchored at both ends.

Progressive, sometimes severe, scoliosis is a problem for many people with OI, and may cause respiratory problems. Bracing is generally not effective, as the force applied may deform the ribs rather than straighten the spine. Spinal rodding may be appropriate in severe cases, if the bone is strong enough to support the rod.

Medications and Other Experimental Therapies. Various minerals and medications have been tested throughout the years to determine if they strengthen bone in OI. Most of these substances have not been proven effective. Recently, the bisphosphonate drugs (currently approved for use in preventing and treating postmenopausal osteoporosis, and bone complications of certain cancers) have been studied and show promise for children and adults with severe OI; research is ongoing. Other treatments, including growth hormones and gene, cell and drug therapies are also being researched.

Healthy Lifestyle. People with OI benefit from a generally healthy lifestyle, including safe exercise and a nutritious diet. Adequate intake of nutrients, such as Vitamin D and calcium (to maintain bone density) and Vitamin C (to promote healing) is important. However, megadoses of these nutrients are not recommended. Evaluation by a physician or registered dietitian will help people with OI determine adequate nutrient intake for their body size and age. Maintaining a healthy weight reduces stress on fragile bones. People with OI should avoid smoking, excessive alcohol or caffeine consumption, and steroid medications, which may affect bone density.

Are There Precautions to Take When Caring for a Person with OI?

- Never pull or push on a limb, or bend it into an awkward position.
- Lift a baby with OI by placing one hand under the buttocks and legs, and the other hand under the shoulders, neck and head. Do not lift the baby from under the armpits, or lift by the ankles to change a diaper. Be aware of where the baby's arms and legs are at all times to avoid awkward positions or getting a hand or foot caught.
- For severly affected babies, it may be helpful to use a baby carrier with a contoured foam insert to transport the child.
- It is important for babies with OI to be held and touched by parents and other caregivers, and that they be allowed to explore independent movement. Supporting infants in a variety of positions (e.g., side lying, stomach lying) develops muscles that will help with sitting and standing later on. Fractures will occur no matter how careful you are, and the physical and emotional benefits of touch and movement usually outweigh the risks.
- Use caution when inserting IVs, taking blood pressure, or performing other medical procedures on children and adults. Pressure on an arm or leg can lead to bruising or fractures.
- When a fracture is suspected, minimize handling of the affected limb.
- Respect the opinions, advice, or instructions provided by parents, older children with OI, and adults with OI. They have dealt with dozens, even hundreds, of fractures and medical procedures, and often have a good sense of whether a fracture has occurred even before x-rays are taken. They have often learned the best methods (medication, positioning, lifting, etc.) to minimize pain and distress when a fracture occurs.

For More Information:

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