

## **LEARNING OBJECTIVES**

- 1) Explain the epidemiology and prevalence of Osteogenesis Imperfecta.
- 2) Describe the typical presentation of Osteogenesis Imperfecta.
- 3) Describe the prognosis and treatment for Osteogenesis Imperfecta.
- 4) Name the genes involved and mode of inheritance for Osteogenesis Imperfecta.
- 5) Name and describe the variations of Osteogenesis Imperfecta.
- 6) Create a genetic counseling plan for a patient and the family members of a person with Osteogenesis Imperfecta.

## **PRETEST QUESTIONS**

1. Osteogenesis Imperfecta is a hereditary disorder affecting which of the following?
  - a) Osteoclasts
  - b) Osteoblasts
  - c) Collagen Type 1
  - d) Calcitriol
  - e) Fibrillin
2. All of the following are symptoms of the disorder EXCEPT?
  - a) Loose joints
  - b) Early loss of hearing
  - c) Bones which fracture easily
  - d) Spinal curvatures
  - e) Increased muscle tone
3. Through what mode of inheritance is Osteogenesis Imperfecta acquired?
  - a) Autosomal dominant
  - b) Autosomal recessive
  - c) X-linked
  - d) Incomplete penetrance
  - e) Multivariant inheritance
4. Osteogenesis Imperfecta usually presents itself at the following ages?
  - a) 0-20
  - b) 21-40
  - c) 41-60
  - d) 60+
5. A person with a form of Osteogenesis Imperfecta has what chance of passing it along to his/her child?

- a) 25%
- b) 50%
- c) 66%
- d) 75%
- e) 100%

**Answers:** 1. c 2. e 3. a 4. a 5. b

## **CASE STUDY**

14 year-old girl presents to her pediatrician's office with low back pain for 2 weeks duration. She denies any history of trauma or other associated symptoms. She reports the pain as constant and achy. Her past medical history includes a Colles' fracture at age 10 and a tibia fracture at age 12. Family History includes a mother and an aunt diagnosed with osteoporosis in their 30's. Her menstrual history is unremarkable. Physical examination is only remarkable for tenderness over the L1-L3 area of the spine, blue colored sclera, and abnormal dentition.

## **DIFFERENTIAL DIAGNOSIS**

Congenital hypophosphatasia, achondrogenesis, Rickets, osteomalacia, congenital brittle bones with joint contractures (Bruck syndrome), congenital brittle bones with craniosynostosis and ocular proptosis (Cole-Carpenter syndrome), juvenile Paget disease, juvenile osteoporosis and child abuse.

## **SYNONYMS**

Van der Hoeve syndrome, trias fragilitas osseum, Eddowe's syndrome, osteopsathyrosis ideopathica of Lobstein, Ekman-Lobstein disease, osteogenesis imperfecta congenita, brittle bone disease.

## **EPIDEMIOLOGY AND PREVALENCE**

Osteogenesis Imperfecta occurs in approximately 1 in 20,000 live births. More than 200 gene mutations have been associated with the OI phenotype. OI is an inherited connective tissue disease that results from mutations in the genes that code type 1 collagen. These genes are COL1A1 and COL1A2. This inability to form normal type 1 collagen can lead to problems forming normal bone, tendon, ligament, skin, and sclerae. Osteogenesis Imperfecta is categorized by types I-IV increasing with severity of disease.

## **PRESENTATION OF OSTEOGENESIS IMPERFECTA**

The presentation of disease varies widely across patient populations. It often varies in severity as you move from type I (mild) to type IV (severe). Common presenting

manifestations of OI include a history of atypical fractures, hearing loss, blue sclera, scoliosis, increased laxity of ligaments, short stature, skull deformities, and easy bruising. With type I OI, fractures can range from none to numerous during a patient's lifetime.

### **Classification**

There are at least 4 types defined. Type I (mild), type II (extremely severe), type III (severe) and type IV (undefined). However, precise typing is often difficult.

#### ***Type I***

This is the classic, non-lethal type with autosomal dominant inheritance. It is the most common type. Patients will usually have blue sclerae, infants will lack fractures at birth and are of normal height. Type 1<sub>A</sub> has abnormal dentinogenesis and type 1<sub>B</sub> does not. Vertebral malalignment and deformation of tubular bones would be unusual in this type. 96% are able to walk, and 35 % are deaf, with the usual onset in childhood or puberty. The recurrence risk is near 50%.

#### ***Type II***

Stillbirth or neonatal death is certain, making this a much more severe form of the disease with many fractures occurring during movement in utero and birth. Limb shortening with crumpled long bones with bowing is usually present. Broad, beaded ribs are present. A small thorax is seen with poor ossification of the skull and blue sclerae. Many of the fetuses will be small for gestational age. The recurrence risk is 10-25%.

#### ***Type III***

This type is characterized by progressive deformity of the long bones and spine and often leads to an early death. These patients may show shortened and bowed long bones and decreased ossification of the skull. The blue sclerae may fade or disappear later in life. With very close similarities to type II, it is very difficult to differentiate at birth when there are also multiple fractures present. Autosomal dominant and recessive inheritance is seen, with a recurrence rate quoted at 7%.

#### ***Type IV***

This is the mildest form. Inheritance is autosomal dominant and their sclerae can fade to white over time as well. Fractures and deformities are rare. The recurrence risk is 50%.

### **PROGNOSIS AND TREATMENT OF OSTEOGENESIS IMPERFECTA**

Once diagnosed, patients with OI should undergo monitoring for potential complications on a regular basis. These tests include a hearing test, DEXA scan to assess bone density, and spirometry. Skeletal radiographs should only be done on an individual basis for

clinical suspicion of fractures. Pediatricians of OI patients should pay particular attention to growth and head circumference, hearing testing, vision testing, and developmental milestone achievement.

Physical and Occupational Therapy can be an essential part of medical treatment and rehabilitation efforts for OI patients. Orthopaedic consultation is almost always necessary in the management of OI patients in relation to management of fractures and assessment of deformities.

Pharmacologic Therapies: Bisphosphonates are often used effectively although they are not specifically approved for use in patients with OI. IV pamidronate has been used in children, but with limited effectiveness. Off label bisphosphonate therapy should be considered on a patient-to-patient basis. Experimental therapies include growth hormone, cell replacement therapy, and gene therapy.

Prognosis: The prognosis often depends on the type of OI and thus the severity of the disease. Type I patients often have a normal life expectancy. However, those patients with more severe types, such as types III-IV often have a decreased life span. This increase in premature deaths may be directly correlated with mortality following hip fractures in OI patients.

## **GENES ARE INVOLVED WITH OSTEOGENESIS IMPERFECTA**

Mutations in the COL1A1, COL1A2, CRTAP, and LEPRE1 genes cause Osteogenesis Imperfecta.

Mutations in the COL1A1 and COL1A2 genes are responsible for over 90 percent of all cases. These genes provide information for making proteins that are used to assemble type I collagen. This type of collagen is the most abundant protein in bone, skin, and other connective tissues that provide structure and strength to the body.

Most of the mutations that cause Osteogenesis Imperfecta type I occur in the COL1A1 gene. These genetic changes reduce the amount of type I collagen produced in the body, which causes bones to be brittle and to fracture easily. The mutations responsible for most cases of Osteogenesis Imperfecta types II, III, and IV occur in either the COL1A1 or COL1A2 gene. A defect in the structure of type I collagen weakens connective tissues, particularly bone, resulting in the characteristic features of Osteogenesis Imperfecta.

Mutations in the CRTAP and LEPRE1 genes are responsible for rare and severe cases of Osteogenesis Imperfecta. Cases caused by CRTAP mutations are usually classified as type VII; when LEPRE1 mutations cause the condition, it is classified as type VIII. The proteins produced from these genes work together to process collagen into its mature form. Mutations in either gene disrupt the normal folding, assembly, and secretion of collagen molecules. These defects weaken connective tissues, leading to severe bone abnormalities and troubles with growth.

The COL1A1 gene is located on the long (q) arm of chromosome 17 between positions 21.3 and 22.1.

The COL1A2 gene is located on the long (q) arm of chromosome 7 at position 22.1.

The CRTAP gene is located on the short (p) arm of chromosome 3 at position 22.3.

The LEPRE1 gene is located on the short (p) arm of chromosome 1 at position 34.1.

## **GENETIC COUNSELING IN OSTEOGENESIS IMPERFECTA**

Genetic counseling should be offered to those parents of a child with OI if they wish to have more children. Due to its Autosomal Dominant Inheritance pattern, 50% of siblings will be affected. Once the mutation has been identified in a patient with OI through collagen biopsy or DNA analysis, molecular genetic testing for the gene should be offered to all siblings. Also, 50% of offspring of those patients with OI will inherit the mutation in the defective gene. If both parents have OI, then there is a 75% chance that the child will be affected. Therefore, all siblings and offspring should be tested for the COL1A1 and COL1A2 gene. Once it is identified that the child or sibling has the same OI-causing mutation, their symptoms can be more or less severe than their affected parent or sibling.

Less commonly, Osteogenesis Imperfecta has an autosomal recessive pattern of inheritance. The parents of a child with an autosomal recessive disorder typically are not affected, but each carry one copy of the altered gene. Some cases of Osteogenesis Imperfecta type III are autosomal recessive; these cases usually result from mutations in genes other than COL1A1 and COL1A2. When Osteogenesis Imperfecta is caused by mutations in the CRTAP or LEPRE1 gene, the condition also has an autosomal recessive pattern of inheritance.

## **PATIENT INFORMATION RESOURCES**

Osteogenesis Imperfecta Foundation

<http://www.oif.org/site/PageServer>

Fast Facts Page

<http://www.oif.org/site/PageServer?pagename=FastFacts>

Osteogenesis Imperfecta Clinic at the Kennedy Krieger Institute Information Page

<http://www.osteogenesisimperfecta.org/>

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