

## Case Report

# BRITTLE BONES, UNBREAKABLE SPIRIT: OSTEOGENESIS IMPERFECTA

Subhra Mandal <sup>\*1</sup>, Prabir Mandal <sup>2</sup>, Panchanan Kundu <sup>3</sup>.

<sup>\*1</sup> Associate Professor, Dept. of Anatomy, Medical College Kolkata , West Bengal , India.

<sup>2</sup> Post Graduate Resident in DNB (PMR), S.N.P. Hospital , Kolkata , West Bengal, India.

<sup>3</sup> Professor & MSVP, Bankura Sammillani Medical College, Bankura, West Bengal , India.

## ABSTRACT

Osteogenesis imperfecta (OI, Fragilitis Ossium or Brittle bone disease) is a group of rare inherited disorders with a broad spectrum of clinical and genetic variability. It is characterized by fragile bones that are prone to fracture often from mild trauma or with no apparent cause. People with OI are born with defective connective tissue or without the ability to make it, usually because of a deficiency of Type1 collagen. Incidence of OI is estimated to be one per twenty thousand live births. Eight types of OI can be distinguished. Most cases are caused by mutations in the COL1A1 and COL1A2 genes. We have reported a special case of OI, probably belonging to Type III group. The subject visited the PMR (Physical Medicine & Rehabilitation) OPD of Bankura Sammilani medical college (BSMC), Bankura ,West Bengal, India.. The details of etiology, diagnosis, genetic causes and treatment will be discussed in the study. Diagnosis of OI is based on clinical features and may be confirmed by collagen or DNA testing. There is no cure for OI. Our management is aimed at increasing over all bone strength to prevent fracture and maintain mobility. Nevertheless, life style modifications by adaptive equipments, oral drugs (Bisphosphonates) and Intramedullary rod insertions, provide a significant degree of autonomy to OI patients.

**KEY WORDS:** Osteogenesis imperfecta (OI), Collagen, Mutations, Bisphosphonates, Intramedullary rod insertions.

**Address for Correspondence:** Dr. Subhra Mandal, Associate Professor, Dept. of Anatomy, Medical College Kolkata, West Bengal , India. Contact No.: +919477458100

**E-Mail:** [drsuvramandal@gmail.com](mailto:drsuvramandal@gmail.com)

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## INTRODUCTION

In 1835, Lobstein coined the term “Osteogenesis imperfecta” [1], which means imperfect bone formation. Earliest known case of osteogenesis imperfecta (OI) in a partially mummified infant skeleton from ancient Egypt is now housed in the British Museum in London. Oakley and Reece (2010) [2] state OI is one of the most prevalent skeletal dysplasias. Incidence of OI is approximately one in every twenty thousand live births (Sillence, 1981)[3].

Osteogenesis imperfecta (OI and sometimes known as brittle bone disease, or “Lobstein syndrome”) is a congenital bone disorder characterized by brittle bones that are prone to fracture. People with OI are born with defective connective tissue, or without the ability to make it, usually because of a deficiency of Type-I collagen. There are eight recognizable forms of OI, whose characteristic features overlap. Most cases are caused by mutations in the COL1A1 and CO L1A2 genes. OI is equally common in both sexes and is found in all races and ethnic groups.

## CASE REPORT

A Hindu boy, Haripada Gorai, aged 15 years, resident of Bankura (village: Pairachali), West Bengal, India, was presented at the Physical medicine & Rehabilitation (PMR) OPD of Bankura Sammilani Medical College with severe skeletal deformity, in the month of August 2013. Though his chief complaint was moderate respiratory distress, characteristic feature was the gross bony deformity of upper and lower limbs along with severe growth failure.

**I. History of present illness:** Patient was apparently normal up to the age of 8 years, except mild forward bending of both tibia. He was able to do his routine chores with the help of a bamboo stick. (Photo-1)

Gradually, over a course of five to six years, upper & lower limb deformities developed, followed by severe growth failure. Actually the deformities were due to repeated fracture and healing. (Photograph-2)

Moderate respiratory distress was the chief presenting complaint, due to gross deformity of rib cage. It started for the last one month. Oxygen inhalation tube can be seen in the photograph-2.

Progressive hearing loss and increased frequency of micturition also appeared later in the course.

**II. Family history & Prenatal history:** Neither the parents nor any other siblings (two sister and one brother), suffered from similar illness. Routine prenatal screening ultrasonography performed during second trimester revealed no significant abnormality Antenatal and postnatal period of mother was uneventful. Subject's mother was non-smoker and there was no history of any special drug intake during pregnancy.

### III. Clinical findings:

- Triangular facies and frontal bossing
- Malocclusion of teeth (Dentino-genesis imperfecta)
- Bluish gray colour of sclera
- Hearing loss (Conductive deafness)
- Barrel shaped rib cage (Pectus carinatum) leading to the presenting complaint of respiratory distress (Photo-3).

f) Scoliosis. (Photo-4)

g) Repeated fractures followed by healing resulting in severe limb deformities. (Photo-5a&5b)

h) Short stature, stunted growth.

i) Laxity of joints and poor muscle tone in arms and legs.

j) Increased frequency of micturition for the last six months.

### Investigations:

Tests	Findings	Normal Values
Hb%	10.8 gm%	12-14gm%
Serum Urea	20mg/dl	20 to 40 mg/dl
Serum Creatinine	0.6mg/dl	0.6 to 1.2 mg/dl
Fasting Blood Sugar	94mg/dl	75-100 mg/dl
P.P. Blood Sugar	120mg/dl	120 to 130 mg/dl
Serum Calcium (Ca <sup>2+</sup> )	10.4mg/dl	8.7 to 10.2 mg/dl
Serum Phosphate (Po <sub>4</sub> )	4.3 mg/dl	2.5 to 4.3 mg/dl
PTH (Parathormone)	40.60pg/ml	8 to 51 pg/ml
TSH (Thyroid Stimulating Hormone)	2.99 µ IU/ml	0.34-4.25 µ IU/ml
Vit D <sub>3</sub> (1.25 hydroxycholecalciferol)	30 pg/ml	15-75pg/ml

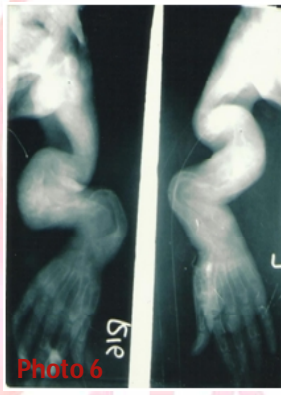
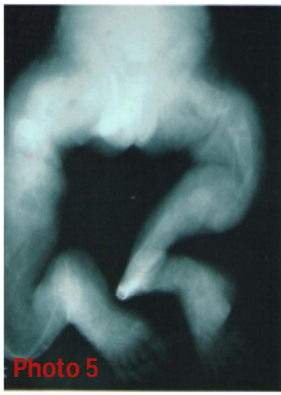
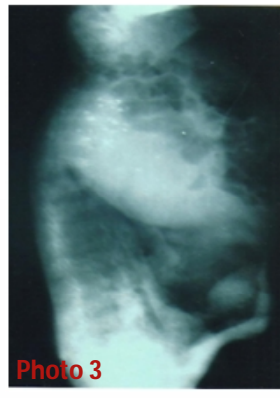
Urine for routine examination and culture sensitivity revealed Escherichia Coli Infection sensitive to Levofloxacin.

USG neck revealed Parathyroid Adenoma.

USG whole abdomen showed Bilateral Medullary Nephro-calcinosis.

## DISCUSSION AND LITERATURE REVIEW

Osteogenesis imperfecta is a group of inherited connective tissue disorders responsible for severe decrease in bone mass that leads to varying degrees of skeletal fragility. Approximately 80% cases of OI are caused by mutations [3]. In the COL1A1 or COL2A2 genes which encode the alpha1 and alpha2 chains of Type-1 collagen respectively. Type-1 collagen is a triple helix formed by 2 copies of alpha1 chain and one copy of alpha2 chain. The COL1A1 gene on chromosome 17 encodes the pro alpha1 chain and the COL2A2 gene on chromosome 2 encodes the pro alpha2 chain. As Type 1 collagen is the most prevalent protein in bone, skin and other connective tissues, so ligaments, sclera, bone & dentin are mainly affected [4].



OI has different classifications that range in severity and affect patients differently. Some have brittle bones without fractures; others have severe bone abnormalities, while many die shortly after birth. Though the most widely used system to classify different types of OI was developed by Sillence et al (1979) [3]; now an expanded revised classification is in vogue (Courtesy-Harrisons Practice of Internal Medicine) [5].

Types	Bone Fragility	Blue Sclera	Abnormal Dentition	Hearing loss	Inheritance
I	Mild	Present	Present in some	Present in most	AD
II	Extreme	Present	Present in some	Un-known	S, rarely AR
III	Severe	Bluish at birth	Present in some	High incidence	AD, rarely AR
IV	Variable	Absent	Absent in IVA, present in IVB	High incidence	AD
V	Moderate to severe	Absent	Absent		AD
VI	Moderate to severe	Absent	Absent		Unknown
VII	Moderate to severe	Absent	Absent	Absent	AR

Expanded Classification of Osteogenesis Imperfecta (OI).

**Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; S, sporadic

Most cases of OI are now known to arise from autosomal dominant mutations which are either genetically inherited or new (sporadic). The inherited mutations have a recurrence risk in subsequent pregnancies of 50% , if a single parent is affected; whereas the new mutations have an unpredictable recurrence risk. A small number of cases previously thought to be autosomal recessive, have now been proved by molecular and linkage analysis to be secondary to gonadal mosaicism. The recurrent risk for these cases is also unpredictable.

OI consists of eight different phenotypes which vary in their severity, with the first four being more prevalent [5]. Rabiee and Etemadi (2011) [6], describe Type I as the most common and mildest forms. It is characterized by near normal height, mild short stature, majority of fractures occurring before puberty and distinctly blue sclera. In Indian population, the bluish gray colour of sclera is due to thinness of the collagen layers of sclera, that allows underlying choroid layers to be seen(Harrison) [5]. Type II produces bones so brittle that it is lethal in utero or shortly after birth.



Death may be due to underdevelopment of lungs caused by rib fractures. Type III is the most severe, nonlethal, progressively deforming type of OI. The typical features are triangular facies, normal sclera, multiple fractures from minor stress leading to progressive deformities, short stature and kyphoscoliosis. The spine deformity can impair respiration, cause cor pulmonale and predispose to pulmonary infections. OI Type IV is a more moderate form with normal sclera, short stature and skeletal deformities that are less severe than those in Type III. Rarer types Type V to VIII of OI are moderate to severely deforming. Type V is recognized by hyperplastic callus formation. Type VI is identified histologically by fish scale pattern of bone lamellation. Rhizomelia and coxa vara are observed in patients with Type VII. Type VIII is characterized by severe growth deficiency, skeletal undermineralisation and bulbous metaphyses.

Cundy (2012) [7] described another associated feature "Dentinogenesis imperfecta", where the enamel of the teeth apparently appears normal, but the teeth may have a characteristic amber, yellowish brown or translucent bluish gray colour; because of a deficiency of Dentin that is rich in Type I collagen. Changes in other connective tissues include thin skin that scars extensively and joint laxity with permanent dislocations (indistinguishable from those of Ehlers -Danlos syndrome).

Borland and Gaffey (2012) [8] described that fractures in OI patients heal at a normal rate; however they have a poor quality callus. Repeated fractures, typically lead to progressive deformity (both shortening and angular). This is due to the poor quality callus being easily deformed by weight bearing forces.

Hearing loss [9] (mild to profound) usually begins during the second decade of life and occurs in more than 50% of individuals over the age of thirty. Deafness may be conductive, sensorineural or mixed, and it varies in severity. The middle ear usually exhibits maldevelopment, deficient ossification, persistence of cartilage in areas that are normally ossified and abnormal calcium deposits.

Lo Mauro et al (2012) [10] reported a study, where rib cage deformities due to OI lead to severe respiratory difficulties. Oakley & Reece (2012)[2] found "scoliosis in OI patients under the age of five years in 26% cases. This percentage increased to 82% in older children. Respiratory complications secondary to chest deformity and scoliosis leads to limitations in thoracic function and make it the principle cause of death in most patients with OI".

Type I collagen comprises approximately 85% of cardiac muscle. Deficiencies in the collagen can lead to major changes in the structure and function of myocardium. Oakley & Reece (2012)[2] discussed the importance of routinely performing echocardiography preoperatively to rule out cardiac abnormalities in high risk OI patients. The most common cardiac abnormality specific to OI was reported to be aortic root dilatation followed by mitral valve prolapse.

Present case belongs to Type III osteogenesis imperfecta according to revised classification provided by Harrison's book of medicine [5]. Following features direct the case to be included in Type III OI: Triangular facies, Dentinogenesis imperfecta, Bluish grey sclera, Hearing loss, Repeated fractures followed by healing, Scoliosis and severe growth retardation. Presenting complaint of respiratory distress was due to barrel shaped rib cage (Pectus carinatum). Only the autosomal dominant pattern of inheritance is not shown by the subject. Probably it is a case of sporadic mutation. The patient arrived very late during the course of the disease, and also the non availability of any special form of treatment (bisphosphonate therapy or corrective surgery like rodding or mobility aids), compelled the attending physiatrists to provide the basic symptomatic treatment only. The patient is totally bed ridden now, dependent upon the care givers.

**TREATMENT:** Individualisation and optimization of OI treatment in adults remain a challenge, because available treatment does not target the underlying collagen defect. Also available literature gives weak support for choice of treatment for adult patients.

Treatment of OI consists of symptomatic medical management to reduce the occurrence

of fractures, physical and occupational therapy to promote gross motor development and maximize functional independence, and surgery to stabilize bones and correct deformities.

### 1. Medication:

a) Bisphosphonates especially Pamidr-onate causes pain relief and prevents the loss of bone mass. This therapy results in sclerotic metaphyseal band formation seen in Xrays. The bands are the result of failure of remodelling of primary spongiosa into secondary spongiosa in the physis (Suresh and Thomas, 2010,p.43) [11].

b) Hormone replacement therapy or selective estrogen receptor modulator therapy is strongly recommended in postmenopausal women with OI [12].

c) Growth Hormone and Parathyroid hormone act as potent bone anabolic agent and research work is going on to include them in the treatment of OI [12].

d) Prophylactic supplementation of Calcium (500-1000 mg) and Vitamin D (400-800IU) help OI patients to overcome the deficiency caused due to repeated fractures and immobilization.

e) Bone pain due to deformities and degenerative lesions, satisfactorily respond to symptomatic analgesics.

f) Gene therapy [12] for OI is complicated by genetic heterogeneity of the disease and by the fact that most of the OI mutations are dominant negative where the mutant allele product interferes with the function of normal allele.

Techniques based on marrow stem cells are currently under research.

### 2. Orthopedic treatment:

A careful preoperative evaluation with special attention to lung function is essential in types III& IV OI. Nicolaou, Bowe, Wilkinsin , Fernandes and Bell (2011)[13] discuss splinting of long bones with the use of intramedullary implants in order to prevent recurrent fractures and allow correction of deformities. Prolonged immobilization is to be avoided after a fracture or a surgical procedure. Early rehabilitation programme designed to reduce the risk of further fracturing is advised. Use of wheelchairs, braces and other mobility aids are also encouraged. Walking with or without mobility aids (wherever

possible), swimming and water therapy are common exercise choices for patients as water allows independent movement with little risk of fractures.

### 3. Life style modifications:

Children and adults with OI will also benefit from maintaining a healthy weight, eating a balanced diet and avoiding activities like smoking or excessive caffeine intake or alcohol consumption or steroid medication. Such things deplete the bone mass making them more fragile and thereby susceptible to fractures.

### 4. Genetic Counseling:

It should be offered to the parents of a child with OI who plan to have subsequent children. During genetic counseling, the possibility that the patient may harbour new mutations, like asymptomatic somatic and gerrmline mosaicism, needs to be discussed.

Prognosis for a patient with OI varies greatly depending on the number and severity of symptoms. Respiratory failure is the most frequent cause of death in OI patients, followed by accidental trauma. Despite repeated fractures, restricted physical activity and short stature, most OI patient's lead productive and successful lives worldwide. In contrast, India tragically lags behind in surgical and mobility aided rehabilitation of OI patients. We still rely on only basic symptomatic management. With the number of OI patients on the rise, its high time, India invested more in research and rehabilitation of OI patients, thereby keeping pace with the rest of the world.

**Conflicts of Interests: None**

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