

## Brittle bone disease - A rare genetic disorder: A case report

Suresh Goyal<sup>1</sup>, Pradeep Meena<sup>2</sup>, Juhi Mehrotra<sup>3\*</sup>, Sunny Malvia<sup>4</sup>, Ravi Rawat<sup>3</sup>, Mahendra Meena<sup>3</sup>, Roshani Dodiya<sup>3</sup>

From <sup>1</sup>Professor and Head, <sup>2</sup>Professor, <sup>3</sup>Resident, <sup>4</sup>Senior Resident, Department of Pediatrics, Rabindra Nath Tagore Medical College, Udaipur, India

**Correspondence to:** Dr. Juhi Mehrotra, Department of Pediatrics, Rabindra Nath Tagore Medical College, Udaipur, India.

E-mail: juhimehra@gmail.com

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### ABSTRACT

Osteogenesis imperfecta (OI) is a group of rare inherited disorders of connective tissue with the hallmark of excessive fragility of bones caused by mutations in collagen characterized by remarkable soft and large cranium and short-curved limbs. Radiological findings, such as, under mineralization of skull, platyspondyly, severely short and deformed long bones, and small continuously beaded ribs, pathognomonic for OI, were observed. Considering the clinical/radiological manifestations, a diagnosis of OI was made.

**Key words:** *Fragilitas ossium, Osteogenesis imperfecta/therapy, Skeletal radiography*

Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disease primarily characterized with osseous fragility and fractures with an incidence of approximately 1 in 20,000 [1]. The spectrum of OI is extremely broad, ranging from the forms that are lethal in the perinatal period to a mild form [1]. Due to its clinical heterogeneity, Sillence classified the disease into four Types, I, II, III, and IV, based on clinical and radiographic findings [2]. Type I OI is the mildest form of the disease, which results from null mutations in COL1A1 or COL1A2 where patients may experience bone fractures but have fewer deformities. Type II OI is the most severe-lethal form; resulting from structural and spontaneous mutations in COL1A1 or COL1A2 in which most of the infants fail to survive either before birth or immediately after birth. Type III and IV forms of OI are progressively deforming, with severe skeletal deformities in some individuals [3,4], inherited in an autosomal dominant fashion.

New additional OI phenotypes, Types V, VI, VII, and VIII [3,5-7], have been added to the list; these phenotypes do not fall into the classical OI phenotypes, originally described by Sillence [2,5,6]. Type V OI is inherited in an autosomal dominant pattern wherein the patients exhibit hyperplastic callus formation and mineralization of the interosseous membrane [6]. Type VI OI has an autosomal recessive form, where patients sustain more frequent fractures than patients with OI Type IV. Types VII and VIII OI result from defects in the prolyl 3-hydroxylation complex [7]. Type VII OI results from defects in cartilage-associated protein, while Type VIII, identified in patients of West African origin, is due to a null mutation in LEPRE1, a gene that encodes prolyl 3-hydroxylase 1 [7].

Other features include blue sclera, otosclerosis with hearing loss, high-arched palate, hyperlaxity of ligaments and skin,

“dentinogenesis imperfecta” (defective dentition), scoliosis, and growth retardation [8]. The major radiographic features are generalized osteopenia, delayed or almost absent calvarial bone formation, platyspondyly (collapsed vertebral bodies), small thorax, continuously beaded ribs, and crumpled and broad tubular bones [9].

### CASE REPORT

A 2600 g term female neonate delivered by a 22-year-old para 2 female was admitted to the newborn special care unit with dysmorphic facies and an abnormal body posture. Her mother received routine antenatal care, iron and folic acid tablets, and calcium supplementation, and pregnancy was uneventful. Prenatal ultrasonography detected rhizomelic shortening of long bones, i.e., both humerus and femur. It was a spontaneous normal vaginal delivery and APGAR score was 7 at 1 min and 8 at 5 min of birth. There was no obstruction, cephalopelvic disproportion which could lead to any fractures during birth. No significant family history shown in the pedigree chart.

Examination of the baby revealed an appropriate, for gestational age, baby weighing 2.6 kg, in a “frog-like position” (Fig. 1). She was pink and afebrile with mild subcostal retractions. Her head, however, appeared disproportionately large, with the circumference of 32 cm (Fig. 2). The ponderal index was 35.09 and also, the anterior and posterior fontanels were palpable, soft, and the sutures were slightly widened. Both lower and upper limbs were short, irregular, and curved medially with extra skin creases. The baby was shown irritated behavior with excessive cry on touch indicating tenderness of limbs and incomplete Moro’s reflex. The baby maintained normal vitals and did not require oxygen support. Investigations



Figure 1: Frog-like position of the newborn, with curved short limbs



Figure 2: The baby on admission with dysmorphic clinical findings: Disproportioned large head, low-set ears, severely shortened limbs, and small chest with protuberant belly

done included an infantogram, full blood count, packed cell volume, white blood cell and differentials, electrolyte, urea, and creatinine. The alkaline phosphatase levels were 181 U/L, serum calcium was 8.55 mg/dL, and phosphorus levels were 4.9 mg/dL. Radiographic examination confirmed the diagnosis of OI.

The infantogram (X-ray) revealed a bell-shaped thorax with widening of anterior end of all ribs; all long bones, showing cortical irregularity with callus formation and deformity, were in the evidence of multiple diaphyseal fractures (Fig. 3). The skull appeared enlarged with increased convolution markings and thinning of the cortex (Fig. 4). All the above findings were in favor of possible OI.

## DISCUSSION

Clinical examination and radiographic assessment of the skull, spine, thorax, limbs, and pelvis are essential to identify the type



Figure 3: Infantogram showing Inferior limbs X-ray with multiple fractures of tibia, fibula and bilateral femur, and upper limb with curved bones, Bell shaped thorax and thinning of cortex of skull bone



Figure 4: Skull appears enlarged with increased convolution markings with thinning of the cortex

of skeletal dysplasia [3]. The studied patient was found to have reduced mineralization of the calvarium, wide open fontanelles, and severe micromelia, with abnormal limb posture and multiple skin creases. Important differential diagnoses consist of OI, thanatophoric dysplasia, hypophosphatasia, campomelic dysplasia, and achondrogenesis Type I. Thanatophoric dysplasia is the most common form of lysergic acid diethylamide; it is characterized by extremely short limbs, macrocephaly, small chest, platyspondyly, and cloverleaf skull in some cases. The femurs are short and curved having typical "telephone receiver" appearance. Ossification of the bones is normal and no fractures are present. However, our patient had severe hypomineralized skull with multiple fractures of the ribs and long bones.

Infantile type - hypophosphatasia manifests *in utero*. It is characterized by severe hypomineralization of all bones, micromelia, and low serum alkaline phosphatase levels [4].

However, in our patient, severe hypomineralization of the calvarium was present with normal alkaline phosphatase values. Clinical and radiological features of our patient were strongly suggestive of OI; classical OI was described with the triad of fragile bones, blue sclera, and early deafness, although, most cases do not have all of these features [10].

Prenatal diagnosis of OI may be performed by chorionic villus sampling with analysis of collagen synthesis of fetal cells between 10 and 12 weeks of gestational age by DNA testing, protein-based testing of the collagen in weeks 12–14, or even by ultrasonography to identify OI Types II, III, and IV. The diagnosis after birth is mainly done with the clinical picture, radiological features, and a significant family history. Severe OI can be detected prenatally by level II ultrasonography as early as 16 weeks of gestation. It is a possibility that OI might be misunderstood as thanatophoric dysplasia. For recurrent cases, chorionic villus biopsy can be used for biochemical or molecular studies. In the neonatal period, the normal to elevated alkaline phosphatase levels present in OI distinguishing it from hypophosphatasia [11].

There is no cure for OI, but there are three types of treatment available: Non-surgical management (physical therapy, rehabilitation, bracing, and splinting), surgery (intramedullary rod positioning), and drugs to increase the strength of bone and decrease the number of fractures. For severe non-lethal OI, active physical rehabilitation, in the early years, allows children to attain a higher functional level than orthopedic management alone. Children with OI Type I and some with Type IV are spontaneous ambulators. In recent years, growth hormone (GH) and bisphosphonate agents have been used in OI therapy. GH is beneficial in patients with moderate forms of OI, showing a positive effect on bone turnover, bone mineral density, and height velocity rate. Bisphosphonates (IV pamidronate or oral olpadronate or risedronate) have proved beneficial in children with severe OI, increasing bone mineral density, and reducing the fracture rate and pain while showing no adverse effects reported. Orthopedic management of OI is aimed at fracture management and correction of deformity to enable function. Fractures should be promptly splinted or cast; OI fractures heal well, and cast removal should be aimed at minimizing immobilization osteoporosis. Correction of long bone deformity requires an osteotomy procedure and placement of an intramedullary rod [12].

Stem cells have generated great interest and excitement because of the potential they possess in regenerative medicine. Application of stem cells to treat OI is attractive; the rationale for treating OI with stem cells is that osteoblasts in the bones of OI patients can be replaced with normal cells that will synthesize normal bone matrix and thus normalize tissue function. This is possible because normal cells will have a growth advantage over the endogenous cells that synthesize defective matrix.

For OI cell therapy, it is not clear which cells are suitable to transplant. A combination of gene and cell therapy may offer the best approach due to the complexity of the OI disease. This is a challenge because methods to direct embryonic stem cells (ESCs) to the desired cell lineages are poorly understood at present. The application of ESCs for OI treatment, therefore, remains a future possibility [6,7].

## CONCLUSION

It is a group of rare inherited disorders of connective tissue with the hallmark of excessive fragility of bones characterized by remarkable soft and large cranium and short-curved limbs. Radiological findings including under mineralization of skull, platyspondyly, severely short and deformed long bones, and small continuously beaded ribs are pathognomonic of OI.

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