

Osteogenesis Imperfecta: a nomenclature

Horacio Plotkin, MD

Inherited Metabolic Diseases Section, Department of Pediatrics, University of Nebraska  
Medical Center, And Children's Hospital, Omaha, Nebraska, USA

Short title: OI nomenclature

Corresponding author: Horacio Plotkin, M.D.

Department of Pediatrics

985456 Nebraska Medical Center

Omaha, NE

68198-5456

Phone: 402-559-4056

Fax: 402-559-4001

e-mail: [hplotkin@unmc.edu](mailto:hplotkin@unmc.edu)

**Abstract**

Background: The most widely used classification of OI divided the disease in four types, although it is now recognized that there are at least 12 forms of OI. These forms have been named with numbers, eponyms or descriptive names. There is a lack of consensus about characteristics of the different types of OI, an effort was made to create a unifying nomenclature for the disease:

Discussion: A uniform nomenclature for OI is presented. Names for different forms of OI proposed are: mild OI with normal stature, moderate OI with short stature, severe OI with triangular face, lethal OI, OI with redundant callus formation, rhizomelic OI, mild OI with extreme joint hyperlaxity, OI with muscle contractures, OI with craniosynostosis and ocular proptosis, OI with optic atrophy, retinopathy and severe psychomotor retardation, OI with microcephaly and cataracts, and OI with dense areas in bones.

Conclusion: The presented descriptive names for different forms of OI will aid in reaching a consensus and a common language for patient care and scientific presentations.

Key words: classification, osteogenesis imperfecta

## Background

The term Osteogenesis Imperfecta (OI) defines a group of conditions with the common feature of brittle bones. It can be defined as a hereditary generalized disorder of connective tissue with bone fragility early in life, often with low bone mass without obvious primary mineral metabolic disturbance. Apart from brittle bones, all other clinical characteristics of OI are variable, and even different members of the same family may present with a different degree of severity [1]. The concept that OI is a disease caused exclusively by mutations in the pro-collagen genes has been left aside, as in many instances mutations of those genes can not be found in patients with clinical picture of OI, and mutations in other loci have been found in others [2]. This disease has received different names through history, including osteopsathyrosis, Vrolik's disease, fragilitas ossium, mollities ossium, Lobstein's disease, and Van der Hoeve syndrome, among others [3]. OI is in fact a heterogeneous group of conditions, and severity ranges in a continuum from mild cases with no deformity, normal stature and no fractures, to forms that are lethal in the perinatal period. In a first attempt to classify OI, in 1906 Looser divided it in two forms [4]: "congenita" (Vrolik) and "tarda" (Lobstein), depending on the severity of the presentation. In OI congenita multiple fractures may occur *in-utero*, whereas in OI tarda, fractures occur at the time of birth or later. OI tarda has also been sub-divided in "gravis" and "levis" [4]. This classification is no longer current because it is considered as an over-simplification of the complex clinical picture of OI. There have also been attempts to classify OI according to radiological characteristics [5]. Some of the features suggested by the authors of this classification are not present until age 5 or 10 years, and children of early ages can not be classified using this scheme. There have also

been attempts to classify OI according to severity [6, 7]. The most commonly used classification divides the patients in four types (I-IV) [8, 9]. In fact, it is now widely recognized that there are more than 12 forms of OI [10, 11]. Some of the forms of OI have been numbered (OI I-VII [9, 12-14]), others have been named with eponyms (Cole-Carpenter syndrome [15], Bruck syndrome [16]), and others with clinical descriptions (OI with denser areas in bones [17], OI with optic atrophy, retinopathy, and severe psychomotor retardation [18], OI with microcephaly, and cataracts [19], etc.). The numeric classification is somewhat confusing, as the characteristics of each type are not clear. There is no consensus about basic characteristics of the different types. For example, it is not clear if an individual with short stature can have type I OI, or if bone deformity rules out the diagnosis of Type I OI. Also, it is not clear if an individual with normal height can have type IV OI. Type II OI is defined as lethal, but there are cases of children with clinical characteristics of type II OI that have survived several years. There are many overlaps among different types making it difficult to classify patients precisely. Furthermore, the current classification does not allow for prognosis, as individuals with type I OI may have numerous fractures and chronic pain in the course of their lives. The OI-pseudoglioma syndrome is now called osteoporosis - pseudoglioma syndrome [20, 21], and for some specialists this is not currently considered a form of OI. This is part of a lack of precision at the time of defining a syndrome as being OI or not. For example, the so-called "Type VI OI" is a syndrome with brittle bones and a defect in bone mineralization. In a recent review, this syndrome was classified as OI, whereas the Cole-Carpenter syndrome, with brittle bones, craniosynostosis and ocular proptosis was

classified as “an entity resembling OI” [22]. It is not clear when a syndrome is OI or not. Here, a new descriptive nomenclature for OI is proposed (Table 1).

## **Discussion**

The proposed names for the different forms of OI are:

### Mild OI with normal stature

The hallmark of this type of OI is normal stature. Individuals have few or no fractures, mostly during the first years of life or even at birth [23]. They are fully ambulatory, and do not have bowing of the long bones or vertebral fractures. Most have blue sclera, but it can be white, or blue color may fade as the individual grows older. This condition is transmitted with an autosomal dominant trait. Despite absence of fractures, bone density can be very low, with no relation with clinical severity, underscoring the relative lack of significance of bone density measurements assessing severity in patients with OI. In many instances bone density is normal during the first months of life, and individuals progressively fail to increase bone mineral density appropriately. Fractures may be present during the first months of life. In some cases the diagnosis is an incidental finding after a fracture [24]. Dentinogenesis imperfecta can be present even in very mild cases, and it has been suggested that this characteristic is useful to distinguish two forms of mild OI [25]. Early hypoacusia [26, 27] and cardio-vascular problems, particularly aortic valvular disease [23] can be present in these subjects. The most common mutation causing mild OI causes a reduction in the production of otherwise normal type I collagen.

### Moderate OI with short stature

These individuals typically have short stature, bowing of long bones, and vertebral fractures, but no triangular face. Scoliosis and joint laxity may be present. Patients with this form of OI are generally ambulatory, but they may need aids for ambulation. Based in the presence of DI, moderate OI has been sub-divided in two forms, a and b [25].

#### Severe OI

These patients have a characteristic triangular face, product of an enlarged head and under-development of the facial bones. They also have chest deformities, short stature, and severe deformities of the long bones, vertebral fractures, and scoliosis. They are frequently wheelchair-bound, although some are able to walk with aids. Prenatal diagnosis is hard but sometimes possible using ultrasonography [28]. Long bones are severely bowed, and altered structure of the growth plates lead to a particular structural alteration of the metaphyses and epiphyses described a "popcorn appearance".

#### Lethal OI

In this form of OI, newborns do not survive the perinatal period. Causes of death are malformations or hemorrhages of the central nervous system [29], extreme fragility of the ribs, or pulmonary hypoplasia [30]. The infants present with multiple intra-uterine fractures, including skull, long bones and vertebrae, beaded ribs, and severe deformity of the long bones [31]. Prenatal differential diagnosis between severe and lethal OI is usually not possible. Extremely severe cases can be born dismembered [32]. The vast majority of cases are autosomal dominant new mutations [33-35]. It has been suggested that there may be different clinical forms of lethal OI [36].

### OI with redundant callus formation

Some patients with OI develop hyperplastic calluses in long bones after a fracture or intramedullary rodding surgery [23]. These patients present with hard, painful and warm swellings over long bones which initially may suggest inflammation or osteosarcoma.

After a rapid growth period, the size and shape of the callus may remain stable for many years [37]. Microscopically there is increased production of abnormal extracellular matrix, that is poorly organized and incompletely mineralized [38]. A series of case reports of hyperplastic callus formation in OI can be found in the literature [4, 37, 39-44] In a series of 60 patients with OI 17% developed hyperplastic callus before the age of 20 years [45]. These large calluses may also be present in flat bones [46].

These patients may also have calcification of the interosseous membrane between radius and ulna, determining a clinical sign, as patients are unable to pronate and supinate the forearm. Histological studies show that the bone lamellae are arranged in a mesh-like fashion, as opposed to a parallel arrangement in patients with other types of OI [12].

Patients with this form of OI have white sclera and no dentinogenesis imperfecta.

Mutations in the pro-collagen genes could not be identified so far. Inheritance appears to be autosomal dominant, with variable penetrance.

### Rhizomelic OI

A particular form of OI with short humerus and recessive inheritance was described in a First Nations community of Quebec [14]. The individuals affected have short humerus and femora . The phenotype is moderate to severe. Fractures may be present at birth, and

the condition courses with early lower limb deformities, coxa vara and osteopenia. The bone in rhizomelic OI is not different to that of mild OI by histomorphometry. The genetic defect has been mapped to the short arm of chromosome 3 by linkage studies [47], where there are no genes that codify for pro collagen.

#### Ocular forms of OI

Three forms of OI with ocular involvement have been described: one variant with optic atrophy, retinopathy, and severe psychomotor retardation [18], another with microcephaly, and cataracts [19] and the OI-pseudoglioma syndrome [48]. As discussed above, the later is now referred to as osteoporosis-pseudoglioma syndrome. A defect is in the LRP5 gene, which encodes for the low-density lipoprotein receptor-related protein 5 has been found in patients with this syndrome [49].

#### OI with mineralization defect

Undistinguishable from moderate to severe OI on a clinical basis, this rare form of OI [13], has a prevalence of about 6% of the OI population. It can only be diagnosed by bone biopsy, where a mineralization defect affecting the bone matrix and sparing growth cartilage is evident. These patients have no DI and no wormian bones. Despite the histological mineralization defect, there are no radiological signs of growth plate involvement. The pattern of inheritance is not clear, but the case of two siblings from healthy consanguineous parents has been described, suggesting gonadal mosaicism or a somatic recessive trait [13]. No mutations of COL1A1 and COL1A2 genes have been

found in these patients, and collagen structure appears to be normal. This form of OI shares several characteristics with fibrogenesis imperfecta ossium [50, 51].

#### OI with craniosynostosis and ocular proptosis

Two boys [15] and a girl [52] with this particular form of OI have been described in the literature. Both boys were normal at birth, but after several months, they developed multiple metaphyseal fractures, associated with low bone density in the entire skeleton and craniosynostosis, hydrocephalus, ocular proptosis, and facial dysmorphism. One of the patients had also hypercalciuria. Neurological development is normal in this form of OI. Both patients were wheelchair-bound at adult age, with very short stature, severe bone involvement and normal intellectual and neurological development [11].

#### OI with congenital joint contractures

First described by Bruck et al in 1897 in an adult patient [16], in this form of OI patients are born with brittle bones, leading to multiple fractures and joint contractures and pterygia (arthrogryposis multiplex congenita) [53, 54]. Wormian bones are present, and inheritance appears to be recessive [55, 56]. In three patients that underwent pro-collagen mutation testing, it was not possible to demonstrate any mutations in the COL1A1 and COL1A2 genes [54]. The basic defect was mapped to locus 17p12 (18 cM interval), where a bone telopeptidyl hydroxylase is located [57]. The mutation leads to underhydroxylated lysine residues within the telopeptides of collagen type I, and therefore to aberrant crosslinking in bone, but not in cartilage or ligaments.

### OI with dense areas in bones

Described in one infant [17] who died shortly after birth and presented with an OI phenotype that differed from the usual lethal form. The skeleton had regions of increased bone density, and this girl had dysmorphic facial features, including loss of mandibular angle low set ears, soft skull, and large anterior and posterior fontanelles. Bilateral upper and lower limb contractures were present with multiple fractures in the long bones and ribs. The ends of the long bones were dense in x-rays. Fetal ultrasound at 28 weeks' gestation showed polyhydramnios and bowed long bones of both upper and lower limbs with healing fractures. The patient died after a few hours and histopathological studies identified extramedullary hematopoiesis in the liver, little lamellar bone formation, decreased number of osteoclasts, abnormally thickened bony trabeculae with retained cartilage in long bones, and diminished marrow spaces similar to those seen in dense bone diseases such as osteopetrosis and pycnodysostosis. Genetic testing showed that the child was heterozygous for a COL1A14321G→T transversion in exon 52 that changed a conserved aspartic acid to tyrosine (D1441Y). Abnormal pro $\alpha$ 1(I) chains were slow to assemble into dimers and trimers, and abnormal molecules were retained intracellularly for an extended period [17].

**Summary:** It is proposed that this nomenclature will aid in a more accurate prognostic description of patients than the current classification in four types.

### List of abbreviations

OI     Osteogenesis Imperfecta

**Competing interests:** none declared'

**Table 1:** proposed nomenclature for OI

Mild OI with normal stature

Moderate OI with short stature

Severe OI

Lethal OI

OI with redundant callus

OI with mineralization defect

Rhizomelic OI

Mild OI with extreme joint hyperlaxity

OI with congenital joint contractures

OI with craniosynostosis and ocular proptosis

OI with optic atrophy, retinopathy and severe psychomotor retardation

OI with microcephaly and cataracts

OI with dense areas in bones

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