

## UP-TO-DATE CLASSIFICATION AND TREATMENT IN OSTEOGENESIS IMPERFECTA

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### Abstract

The term of osteogenesis imperfecta (OI) includes a heterogeneous group of genetic disorders of connective tissue and has as the main form of expression recurrent fractures, skeletal fragility and deformity. OI is one of the most common skeletal dysplasias. The disease has an etiology related directly or indirectly to type I collagen, the most important protein of the bone extracellular matrix. The diagnosis of OI is based on history and clinical examination associated with genetic analyses, imaging and laboratory investigations. OI is a disorder which has many clinical manifestations, some of these are present only in certain types of the disease, some characteristics being age-dependent. There is no cure for OI. Treatment is aimed at increasing bone strength to prevent fracture, the surgical correction of deformity, minimizing pain and maximizing mobility and independent function.

**Key words:** osteogenesis imperfecta, COL1A1, COL1A2, pamidronate, classification

### Etiology and classification

The term of osteogenesis imperfecta (OI) includes a heterogeneous group of genetic disorders of connective tissue and has as the main form of expression recurrent fractures, skeletal fragility and deformity [1]. OI is one of the most common skeletal dysplasias.

The disease has an etiology related directly or indirectly to type I collagen, the most important protein of the bone extracellular matrix [2]. In most cases, 90%(classical types), OI is caused by a autosomal dominant mutation in the COL1A1 gene on chromosome 17 or the

COL1A2 gene on chromosome 7, that encode type I collagen [3]. In 10 percent of cases it is believed that OI (non-classical types) is caused by recessive mutations in other genes, that encode proteins from collagen structure: prolyl 3-hydroxylase (P3H1, encoded by the LEPRE1 gene), cartilage-associated protein (CRTAP gene) and peptidyl-prolyl isomerase cyclophilin B (CypB, encoded by the Ppib gene). Sometimes, OI is not inherited but is caused by a gene mutation occurred spontaneously at childhood (de novo mutation). In this case none of parents is affected. Changes in the collagen can be qualitative (defective collagen structure) or quantitative (insufficient amount of collagen).

The classic clinical forms of OI comprise Lobstein's type and Vrolik's type. The first has a variable symptomatology, with a greater or lesser degree of deformity and onset of fractures during growth and adulthood. The second is a severe form that is observable from birth, with frequent intrauterine fractures and a high mortality rate [4].

Because of the clinical variability in OI, more authors [5] have attempted to classify this disease. First classification, which is still used today, was introduced by the Australian physician David Sillence (the "Sillence classification") in 1979 [6] and classifies the disease in 4 types (I-IV). This was based on clinical and radiological findings of OI. In 2004 the Lancet published a new classification: "expanded Sillence classification" which recognizes seven types of OI (I-VII) and in 2007 was proposed an additional type VIII (table 1).

Table 1. Sillence Classification expanded with OI VIII type as proposed by Rauch (2004) and Cabral (2007) [5].

OI type Sillence classification expanded	Clinical severity	Mutated gene	Mode of inheritance
I	Mild-non deforming	COL1A1/2	AD
II	Perinatal lethal	COL1A1/2	AD
III	Severely deforming	COL1A1/2	AD
IV	Moderately deforming	COL1A1/2	AD
V	Moderately deforming	Unknown	AD
VI	Moderately to severely deforming	Unknown	AR
VII	Moderately deforming	CRTAP	AR
VIII	Severely deforming to perinatal lethal	LEPRE1	AR

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In recent years, a molecular genetic classification of OI contains 12 types that display either autosomal -dominant or autosomal-recessive patterns of inheritance and exhibit broad variations in clinical severity [7].

Type I of OI is mild as severity, without progressive deformity, type II is lethal and type III is severe with progressive bony deformity and characteristic facies. Type IV is less well defined and has phenotypic range between types I and III. All of these types are associated with bone fragility, kynetic development delay and growth retardation of varying degrees, depending on the severity of the disease.

#### Diagnosis

The diagnosis of OI is based on history and clinical examination associated with genetic analyses, imaging and laboratory investigations. It may be difficult to make a clinical diagnosis of the milder forms of OI in infancy and childhood. Some patients have a family history of osteogenesis imperfecta, but most cases are due to new mutations [8]. The most important dates in the history and physical examination of patients with OI include: a detailed family history of bone disease, the presence of fractures detected in utero or in the neonatal period; the nature, chronology, and outcome of subsequent fractures; growth velocity, current height and skeletal proportions; the presence and progression of bone deformity. The distinction between mild, moderate, and severe types of disease is based on the number of fractures, the degree of bones deformity and growth impairment, and the age at which the disease is first recognized.

#### Clinical Features

OI is a disorder which has many clinical manifestations, some of these are present only in certain types of the disease, some characteristics being age-dependent. The clinical features of OI, in addition to fractures after minor trauma, may include the following:

- The blue sclerae (50 percent of cases).
- Dentinogenesis imperfecta, characterized by transparent, discolored, and fragile teeth that fracture easily (50 percent of people with OI, particularly in those with the severe forms).
- Bone malformations: pectus carinatum, pectus excavatum, abnormal rib shape, curving of the long bones, vertebral compressions, scoliosis, kyphosis.
- Osteopenia or osteoporosis ( x ray or bone density tests-DEXA).
- The head circumference may be greater than average and the head may appear large relative to the person's small body.
- A triangular facial shape is characteristic in the more severe forms.
- The fontanels may close later than usual.
- Hearing loss which starts in the young adult (about 50% of patients with type I OI have deafness by age 40 years).
- The body may be disproportional.
- The joints may be lax and unstable and the feet may be flat.

- Wormian bones are present in the skull (60 percent of cases).
- Children have decreased muscle mass and associated muscle weakness.
- Motor development may be delayed due to fractures and muscle hypotonia.
- The intellect is normal.
- In some cases exuberant callus formation may occur, which usually follows a fracture or a surgical procedure (OI Type V).

#### Investigations

OI is usually a clinical diagnosis but performing additional investigations may provide useful information in cases where there is some uncertainty and will often help guiding the management [8].

Prenatal testing is possible and indicated for high risk pregnancies (if the mutation has been identified at a relative), being made through the analyse of the collagen synthesis from the fetal cells obtained at 12 weeks villi sample or amniocentesis. Prenatal screening ultrasonography, performed during the second trimester, in severe cases of OI, may show: bowing of long bones, fractures, limb shortening, and decreased skull echogenicity.

Bone radiological investigations may show: osteopenia (low bone density) or osteoporosis, fractures (new, subclinical, or old-healing), bowing of the long bones, vertebral compressions, and wormian bones in the skull sutures (in 60% of patients with OI).

DEXA (Dual Energy X-ray Absorptiometry) provides information about bone quantity, not quality. A low mineral density might be prognostic for a predisposition to fracture. Bone mineral density may be lower than normal in people with any type of OI. At children Z score is used for the interpretation of results [9].

Bone Biopsy of the iliac bone can identify all types of OI. Unfortunately a bone biopsy is a invasive procedure, requiring general anesthesia and specially trained personnel for processing the sample and read the slides. A child must weigh at least 10 kilograms to be a candidate for the procedure. A bone biopsy may be obtained during orthopaedic surgery.

Laboratory testing (for the dominant and recessive forms of OI):

- Collagen molecular testing - a DNA-based analysis of COL1A1 and COL1A2 genes from a blood or saliva sample,
- Collagen biochemical testing - a protein-based analysis of cultured fibroblasts from a skin sample,
- Separate studies that utilize a skin biopsy and sequencing of the genes for cartilage-associated protein (CRTAP) and prolyl 3-hydroxylase (LEPRE1) to test for the recessive forms of OI (when the molecular and biochemical testing are normal in a child with clinically diagnosed OI)

#### Differential Diagnosis

Other medical conditions that share some of the same clinical signs as OI should be excluded. Among them: hypophosphatasia, juvenile Paget's disease, rickets, idiopathic juvenile osteoporosis, some inherited defects in

vitamin D metabolism, Cushing's disease, and calcium deficiency and malabsorption. Ehlers-Danlos syndrome types VIIA and VIIB, which are characterized by lax ligaments and loose joints, can also predispose a person to fractures.

### Treatment

There is no cure for OI. Treatment is aimed at increasing bone strength to prevent fracture, the surgical correction of deformity, minimizing pain and maximizing mobility and independent function. Treatment strategy is multidisciplinary, involving a team of endocrinologist, orthopedist, surgeons, psychiatrists, dentists etc. Methods of treatment currently prescribed include the following:

- behavioral and lifestyle modifications to avoid situations that may cause a fracture,
- orthopaedic surgery,
- scoliosis management,
- physical rehabilitation through physiotherapy and hydrotherapy (strengthen muscles and improve mobility in a gentle manner) [10],
- adaptive equipment and ambulation aids (wheelchairs, braces, and other aids),
- weight management,
- pain management,
- pharmacological treatment with bisphosphonates (a 'standard care' for children with OI),
- treatment with GH.

#### Pharmacological treatment

Treatment with intravenous bisphosphonates was first suggested as treatment to improve bone fragility in children with severe OI in 1987 and it has rapidly become a standard of care [11]. When administered either orally or parenterally, bisphosphonates rapidly bond to hydroxyapatite crystals in bone and, by decreasing osteoclast activity and number, inhibit bone resorption and reduce bone turnover [12]. Another important effect of this treatment is the improvement in bone pain, well-being and longitudinal growth, increase in vertebral and long bone mass with a reduced fracture rate [13].

Cyclic intravenous treatment with pamidronate is the only treatment authorized in many countries for use in children with OI. There is no clear consensus on dose, frequency of dosing, dose adjustment and when to discontinue treatment in OI [13, 14]. The protocol used in Romania recommends the beginning of the treatment at children over 2 years old with a dose of 1 mg/kg/day 3 consecutive days, administered with an intravenous slow infusion. The cure is repeated every 3 months for 2-4 years [13]. Data from the literature suggest that the greatest gain in the bone density is obtained after 2-4 years of therapy. At any rate, in the opinion of many specialists, it does not seem advantageous to stop bisphosphonates treatment in growing children. Pamidronate is a member of the bisphosphonate family of drugs, which are potent antiresorptive agents. They interfere with the mevalonate pathway of cholesterol biosynthesis in osteoclasts, inhibiting the function of these cells but not usually leading to apoptosis, as was believed previously. Rehabilitative therapy together with adequate Ca

and P intake during this treatment could be another way to prevent fractures caused by bone fragility.

A hormone with a favorable effect on bone metabolism is GH who has a positive effect on bone growth and bone turnover by stimulating osteoblasts, collagen synthesis, and longitudinal bone growth [15]. In osteoblast cultures, GH has also shown a positive action on collagen metabolism, by stimulating the expression of insulin-like growth factor 1 (IGF1) and IGF-binding protein 3 (IGFBP-3), which in turn regulates the synthesis of type I collagen. However, there is limited literature data regarding recombinant human GH (rGH) experience in OI. At this time, GH is not found in the standard treatment guidelines in OI [12].

Other therapeutic options were [13]:

- Human recombinant PTH (Teriparatid) which has not been approved for children use because of the osteosarcoma risk.
- Bone marrow transplant: the hematopoietic bone marrow contains osteoblast precursors, but for supporting the fibroblast production a very large quantity is needed; also the immunosuppressive therapy required for every transplant can be itself a source of bone destruction.
- The gene therapy is nowadays in experimental state on animals; its purpose is to block a mutant allele at the COL1 gene and not to interfere with the expression of a normal allele (prevents the translation of a gene responsible for a collagen defect), so a severe form of OI can be transformed in a moderate form.

#### Orthopaedic surgery

- The goals of orthopaedic treatment include fracture care and prevention or correction of bone deformities.
- The use of bracing, splinting, and orthotic supports have an important role in treatment.
- Insertion of intramedullary rods or nails (typically in the lower limbs) is the commonest surgical procedure in OI [8]. Indications include prevention of recurrent fractures and correction of deformity (with osteotomies). The commonest indication for spinal surgery is prevention of scoliosis progression. Details of management depend on the severity of the scoliosis and the age of the patient.

#### Rehabilitation, physical therapy, occupational therapy, nutrition and physical activity

- Most children with OI benefit from physical activity programs. They should include muscle strengthening, aerobic conditioning, and, when possible, protected ambulation.
- Positioning is important to avoid contracture and malformation. It is important not to leave a child with OI in a fixed position, either recumbent or sitting, for long periods.
- Postfracture therapy is necessary to reduce the effects of immobilization on bone density and strength.
- The goal of physical therapy should be to improve function, fitness, and independent movement [10].
- The nutrition goals for individuals with OI are the same as for any individual: to achieve optimal health by taking in adequate calories to achieve and maintain a healthy weight [16].

### Conclusions

OI is a genetic connective tissue disorder that involves multiple organ systems, can affect an individual's function as they age. Most physicians will see very few people with

this disorder during their careers. Despite the need for multiple interventions, adequate treatment of patients with OI can provide acceptable functional outcomes.

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