PRIMEVIEW

OSTEOGENESIS IMPERFECTA

nature REVIEWS DISEASE PRIMERS

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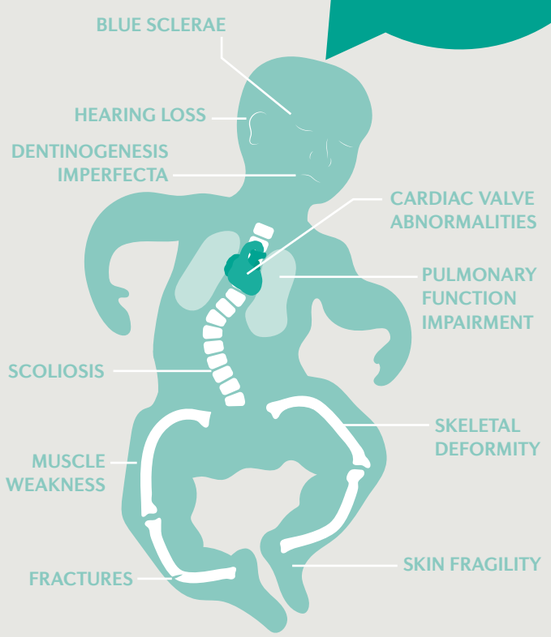
Osteogenesis imperfecta — also known as brittle bone disease — is a phenotypically and genotypically heterogeneous group of inherited bone dysplasias.

DIAGNOSIS

The incidence of osteogenesis imperfecta is estimated at 1 per 10,000 individuals. Diagnosis usually depends on family history and clinical presentation with a fracture (or fractures) during the prenatal period, at birth or in early childhood. Although the primary clinical manifestation involves the skeleton, osteogenesis imperfecta is a generalized connective tissue disorder.

In a minority (~15%) of cases, the disorder is caused by dominant, recessive or X-linked mutations in genes encoding proteins involved in collagen metabolism or bone formation

Prenatal ultrasonography imaging enables the detection of the more-severe types of osteogenesis imperfecta in the second trimester of pregnancy



MECHANISMS

Impairment of collagen synthesis and structure
COL1A1 and *COL1A2*

Autosomal dominant mutations in the genes encoding type I collagen (*COL1A1* and *COL1A2*), affecting collagen structure or quantity, are the main cause of osteogenesis imperfecta

Abnormal collagen post-translational modification
CRTAP, *P3H1*, *PPIB*, *TMEM38B* and *SPARC*

Compromised collagen processing and crosslinking
SERPINH1, *FKBP10*, *PLOD2*, *BMP1* and *MBTPS2*

Altered osteoblast differentiation and function
SP7, *TMEM38B*, *WNT1*, *CREB3L1*, *SPARC* and *MBTPS2*

OSTEOBLAST

Compromised bone mineralization
IFITM5 and *SERPINF1*

BONE

Several types of osteogenesis imperfecta are perinatally lethal. In addition, the life expectancy of individuals affected by the severe, non-lethal types of osteogenesis imperfecta is reduced by 7–10 years compared with the general population, with ~25% of the deaths occurring before 35 years of age

Type I collagen is the major protein component of the extracellular matrix in bone, tendon and skin

QUALITY OF LIFE

The physical domain of quality of life is lower in children with osteogenesis imperfecta than in age-matched controls, mainly owing to pain, fractures, scoliosis, activity limitations and participation restrictions. The quality of life of caregivers is also impaired compared with the general population, especially in the environmental domain, which includes accessibility to health and social care and opportunities for participation in leisure activities.

MANAGEMENT

No cure exists for osteogenesis imperfecta. Management is symptom-based and depends on the type and severity of complications. Musculoskeletal interventions mainly focus on rehabilitation, orthopaedic surgery and pharmacological treatment with anti-resorptive agents (that is, bisphosphonates). Extraskeletal manifestations should be monitored and treated according to organ-specific guidelines.

One of the challenges associated with improved survival is that patients need to transition from their paediatric care team to individual adult providers, who might not have the same level of expertise

OUTLOOK

The classic classification of osteogenesis imperfecta — the Sillence classification — recognizes four distinct groups based on clinical presentation and pattern of inheritance. However, this type of classification does not include newly identified genetic variants, so new systems have been introduced. A genetic classification system has the advantage that the cause of the disorder is clear and that the type does not change over time. However, as most management decisions are made on clinical grounds, a clinical classification system can supplement the genetic system.

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