Osteogenesis imperfecta

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Abstract

Osteogenesis imperfecta (OI) describes a group of rare heritable disorders of connective tissue characterized by varying degrees of low bone mass and increased susceptibility to fractures. Most cases of OI are due to heritable defects in the synthesis or metabolism of type I collagen. The resulting bone tissue is prone to fracture due to a combination of alterations in both material and architectural qualities. The range of OI encompasses antenatal lethality to individuals with only small numbers of fractures. There are various classifications of OI, some of which have expanded along with understanding of the genetic diversity of rarer forms of OI. Accurate diagnosis at the earliest opportunity is important because specialist multidisciplinary input can dramatically improve outcomes in both the short and long term. Bisphosphonates are widely recognized as standard of care in childhood OI but the maximum benefits are only realized alongside the delivery of a multidisciplinary package of care including physiotherapy. There should be a planned and timely transfer of care to an appropriately skilled team based in adult services.

Keywords bisphosphonates; bone; collagen; dual energy X-ray absorptiometry; non-accidental injury; osteogenesis imperfecta

Introduction

Osteogenesis imperfecta (OI) describes a group of rare heritable disorders of connective tissue characterized by varying degrees of low bone mass and increased susceptibility to fractures. The range of OI encompasses antenatal lethality to individuals with only small numbers of fractures. OI occurs in all races and is the commonest cause of primary osteoporosis with an incidence of between 1 in 10,000 and 1 in 20,000. Accurate diagnosis at the earliest opportunity is important because specialist multidisciplinary input, including specific medical therapy, can dramatically improve outcomes in both the short and long term. In England there is now a nationally commissioned service for children with "severe, complex and atypical" OI.

Pathology and pathophysiology

Most cases of OI are due to heritable defects in the synthesis or metabolism of type I collagen. The resulting bone tissue is prone to fracture due to a combination of alterations in both material and architectural qualities. Whilst type I collagen fibres contribute directly to the ductility (a solid material's ability to deform under tensile stress) and toughness of bone, the constituent type I collagen molecules also play roles in mineral crystal formation, extracellular matrix biosynthesis and osteoblast function. Consequently, bone growth is impaired and bone tissue in OI is typically hypermineralized with increased bone turnover, degraded bone microarchitecture (thinner cortices and disruption of trabecular connectivity) and increased numbers of osteocytes.

Type I procollagen is constituted by two proα1 (I) chains and one proα2 (I) chain, coded for by the genes *COL1A1* and *COL1A2*, respectively. Each procollagen chain is largely composed of a repeating sequence of amino acids in the order glycine-X-Y. The chains align and combine into a triple helix. Processing to type I collagen includes cleavage of the N- and C-terminal propeptides. The vast majority of individuals with OI ($\sim$90%) have a mutation of either *COL1A1* or *COL1A2*. Typically, mild forms of OI are caused by stop, frameshift or splice site mutations that result in a quantitative defect of type I collagen production. More severely affected individuals usually have a point mutation affecting a conserved glycine in either *COL1A1* or *COL1A2*, resulting in qualitatively abnormal collagen. Whilst most cases of OI are due to mutations in *COL1A1* or *COL1A2* with autosomal dominant inheritance, some cases, particularly lethal and severe forms of OI, are recessively inherited. Over the last decade, mutations in various genes have been found in individuals with a range of OI phenotypes, complicating classification based on genetics alone.

Classification

The clinical classification of OI proposed by Sillence and colleagues has been widely adopted. Essentially, OI type I is "mild", 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 than the others as it encompasses the phenotypic range between types I and III. The various types are all associated with bone fragility, motor delay and growth retardation (degree tracking with severity). However, within each type, other features are variable, such as ligamentous laxity, presence of Wormian bones, dentinogenesis imperfecta and hearing loss (not usually in the first decade). Sclerae typically remain blue in types I and III.

Characteristic histology and clinical phenotype distinguished three further distinct types of OI, commonly referred to as types V, VI and VII. OI type V is characterized by autosomal dominant OI of moderate severity due to a mutation in the 5′ untranslated region of *IFITM5*. Clinical features include hypertrophic callus formation following fracture, interosseous membrane formation causing limited forearm pronation/supination and bowing deformity of the forearm associated with radial head dislocation. Radiological features are distinctive (see later). In our experience, cases of OI type V develop vertebral crush fractures in the first 2 years of life. Progression of scoliosis is more rapid than in other moderately severe OI cases. OI type VI is a recessively inherited progressive deforming disease of moderate severity. Most cases are due to mutations in *SERPINF1* (encodes the secreted protein, pigment epithelium derived factor (PEDF)). Affected individuals with type VI OI may respond poorly to bisphosphonates. OI type VII is moderately to severely deforming and characterized by rhizomelia and coxa vara. It is caused by a specific splice site mutation in *CRTAP* (encoding cartilage-associated protein). Further rare cases of severe recessively inherited OI have been shown to be due to mutations in the genes encoding the other two components of the prolyl 3 hydroxylase complex (*LEPRE1* and *PPIB*) as well as in genes encoding other

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proteins involved in the post-translational processing of type I procollagen (e.g. SERPINH1, FKBP10). Mutations in the regions of *COL1A1/COL1A2* encoding the C-propeptide of type I collagen and in *BMP1* (BMP1 is involved in the cleavage of the C-terminal propeptide) can result in high bone mass OI phenotypes, emphasizing the fact that a normal (or high) bone mineral density measured using dual energy X-ray absorptiometry (DXA) does not rule out OI. Over recent years even more genes have been identified in cases of OI, broadening the pathophysiology of OI. A current international classification of OI maintains a fundamentally clinical approach, which is helpful for the clinician in the face of such genetic diversity (Table 1). However, it may be the case that as new therapeutics emerge the clinical relevance of a more specific diagnosis may increase.

Clinical assessment

Identification of OI is largely based on history and clinical examination with confirmatory or supplemental evidence provided by imaging and other investigations. The functional and social needs of the child and their family should always be considered.

History

A good history is essential to the diagnosis of OI. It is important to identify features that may suggest alternative diagnoses (including secondary osteoporosis) and to consider other factors that may explain or contribute to bone fragility.

Fractures and dislocations

It may or may not be straightforward to establish whether a child has bone fragility. As a guide, the International Society of Clinical Densitometry has produced a series of statements that try to encapsulate current expert opinion (http://www.iscd.org/official-positions/2013-iscd-official-positions-pediatric/). These state that osteoporosis in childhood is generally indicated by the presence of a clinically significant fracture (i.e. a vertebral crush fracture) or a significant fracture history together with a low bone mineral density. The key to a significant fracture history is the number and site of fractures along with a history of "minimal" trauma. A clinician must therefore seek to identify the number of fractures and dislocations, when they occurred and the site and mechanism for each e.g. a history of recurrent lower limb fractures starting early in life should raise suspicion of bone fragility. Verification of fractures and of details of orthopaedic interventions can be useful.

Modified extract from clinically-based classification of osteogenesis imperfecta (OI) by the International Nomenclature Group for Constitutional Disorders of the Skeleton (INCCDS) 2010 (Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A;155A:943–968.)

Syndrome names[a]	Equivalent numerical type
OI, non-deforming form ("mild")	I
OI, moderate form	IV
OI, with calcification of the interosseous membranes and/or hypertrophic callus	V
OI, progressively deforming type	III
OI, perinatal lethal form	II

[a] Syndromes listed roughly in order of increasing severity.

Table 1

Back pain

Back pain (often described as "stiffness") can indicate vertebral pathology, although children may have multiple vertebral crush fractures with no history of pain. Timing of symptoms, severity (including use of analgesia), location, whether they result in any restriction and their relationship to exercise and sleep are important.

Development, mobility and daily living

Even children with mild forms of OI often start to walk only after the age of 12 months; in those more severely affected the delay can be considerably greater. Apart from interruptions to opportunities for normal development, such as those that arise from fractures and hospitalization, causes of delay in motor development include joint hypermobility, muscle weakness, bone pain and deformity. In the ambulant child, one should enquire about the distance that the child can walk without resting and whether they can run and keep up with peers. In the non-ambulant, one should assess the degree and nature of any independent mobility. Functional consequences of the condition that may impact on a child's schooling or socialization should be actively sought, including both problems of mobility and difficulties in fine motor tasks. In all children there should be enquiry about the amount of assistance required from caregivers, use of aids, adaptations and engagement with local therapy and orthotic services. It is important to understand the degree of variability of any limitations in order to fully understand a child's and family's needs.

Rest of history

Many mildly affected individuals have a relevant family history. Features to enquire about include: short stature; recurrent fractures and/or dislocations; teeth that chip, crack or wear easily; hernias; early-onset osteoporosis; and hearing loss. It is important to identify any consanguinity.

Given the risk of complications such as basilar invagination in OI, it is important to be alert to symptoms that may suggest cord compression or hydrocephalus, such as increasing clumsiness, swallowing problems or headaches that are worse with straining, sneezing or on waking.

Examination

It is important to recognize that general examination of a child with OI type I may reveal no definitive findings to justify the diagnosis, particularly early in life.

Scleral colour is variable and can be difficult to assess although blueness is often obvious, even sometimes dark grey in severely affected cases. Some minor blueness is common in normal children and therefore of little if any diagnostic value, especially in the first 6 months of life.