Osteogenesis Imperfecta– A Tale of 50 Years

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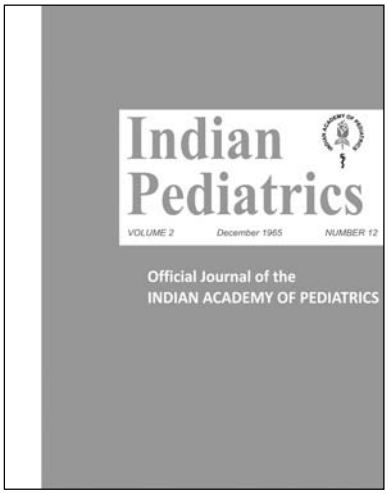
The December 1965 issue of *Indian Pediatrics* had three original articles related to psychoneurosis in the young, osteogenesis imperfecta, and disorders of anomalous fusion of skeleton. Amongst these, we decided to review the article on osteogenesis imperfecta (OI) for this series. Much progress has occurred in understanding of various aspects of OI and its management since the publication of this article fifty years ago.



THE PAST

This *Case Series* by Shrivastava, *et al*. [1] from Gandhi Medical College, Bhopal, presented 7 cases of OI among 16 members of two unrelated families. Through this article, the authors attempted to study the familial pattern of inheritance of OI. In the first family, the index case (case 1) was a 2-year-old girl, fourth in birth order, who presented with inability to walk and lower limb bony deformity. She had a history of recurrent fractures since day 5 of life. She had blue sclera, and her hearing was normal. The serum levels of calcium, inorganic phosphate and alkaline phosphatase were normal while the skiagram of bones revealed osteoporosis with deformity. On eliciting the family history, her elder brother (8 years; case 2) had blue sclera and deafness secondary to otosclerosis, while the elder sister (6 years; case 3) had only blue sclera. There was no evidence of fracture or deformity in either of the siblings. The parents and one of the siblings (4½-year-old) in this family were unaffected. In the second family, the index case (case 4) was a 12-year-old boy with progressively worsening deafness, blue sclera and past history of recurrent fractures. His mother (case 5) died at the age of 22 years during childbirth, and the female offspring (case 6) who apparently had deformities at birth, succumbed on 5th day of life. Both had blue sclera. The father was healthy. The maternal uncle (16 years; case 7) also had blue sclera but no evidence of fractures, deformity or deafness. The exact mode of transmission could not be elicited in both families as complete family history was not available, but a strong familial tendency of the disease was suggested. The cardinal triad (blue sclera, deafness and brittle bones) was not seen in all cases, while the blue sclera was reported as consistent finding. The combination of blue sclera and fracture was more common as compared to deafness. Among the 7 cases reported, 2 fitted into the more severe congenital variety and the rest into the milder tarda form, as per the accepted classification of OI at that time. The family tree revealed that the incidence of deep blue sclera and fractures increased with subsequent pregnancies. The outcome of the congenital variety was poor as mortality occurred early, while the tarda type did well later in life.

Historical background and past knowledge: OI is a clinical entity known since 1000 BC, evident through an Egyptian mummy of an infant kept in London's museum. The medical literature on this disorder can be recognized ever since the seventeenth century, when various alternative terms – like osteomalacia congenita, mollities ossium, fragilitas ossium, and osteopsathyrosis idiopathica – were used to describe it. The term 'osteogenesis imperfecta' was first coined by Lobstein in 1835. In 1906, Looser categorized OI into congenital (Vrolik) and tarda (Lobstein) varieties based on clinical severity [2]. The congenital variety was a more severe form that presented with intrauterine fractures, while the tarda variety followed a milder course, often complicated by otosclerosis with advancing age. The tarda variety was subsequently further divided into gravis (fractures occurring in infancy) and levis (fractures in late childhood) type by Seedorff in 1949 [3]. The characteristic triad of blue sclera, hearing loss and brittle bones was established as distinguishing diagnostic feature of OI by this time. The most accepted hypothesis regarding pathogenesis of OI was impaired maturation of collagen and a defect in osteoblastic activity transmitted by autosomal dominance.

THE PRESENT

Over time it became evident that OI had a wider clinical spectrum than hitherto realized. Sillence [4] in 1979, more than a decade after publication of the above article, proposed and published a new classification of OI to cover its spectrum: type I-mild; type II-lethal; type III-severely deforming; and type IV-moderately severe. At this point of time, the disorder (all types) was considered to be due to presence of abnormal collagen type 1 protein secondary to a dominant mutation in *COL1A1* and *COL1A2* genes encoding the α1 and α2 chains. With new genetic mutations being discovered, new OI types were defined (up to types XIV) which exhibited phenotypic resemblance to types II-IV [5]. In 2013, a new nomenclature that defines five syndromic OI groups along with causative genes has been put forward [6].

Besides the classical triad, other distinguishing features in OI are dentinogenesis imperfecta, ligamentous laxity, bone deformation and short stature. The systemic features associated with morbidity and mortality include basilar invagination leading to potentially lethal neurological outcome, aortic root dilatation, mitral valve prolapse, and restrictive lung disease secondary to scoliosis. There exists wide variation in clinical characteristics of different types of OI, among people with the same type of OI, and even within members of the same family with a particular type of OI.

The most common mode of transmission is autosomal dominant (90%) while a recessive (10%) pattern of inheritance has also been identified in some families. In 2006, Barnes, *et al*. [7] described the first autosomal recessive OI (type II) due to *CRTAP* mutations, and several others have been recognized subsequently. The cases of OI without suggestive family history can be explained by *de novo* mutations or germ cell mosaicism. The various mutations in OI either lead to production of defective collagen which is susceptible to tissue proteolysis, or there is reduced or absent production of normal collagen protein. Besides qualitative and quantitative impairment in the bone matrix, there is inability of the differentiated osteoblasts to mineralize the matrix. This generates mechanically weak bones liable to fractures.

The diagnosis of OI is primarily based on clinical features and radiological signs coupled with a positive family history. Osteopenia of prematurity, hypophosphatemia, idiopathic juvenile osteoporosis and non-accidental injury are close differentials of OI. Skeletal survey in OI reveals osteoporosis, cortical thinning, popcorn calcification, wormian bones in skull in addition to detection of occult and healed fractures and deformities. The confirmation of diagnosis of OI requires molecular testing with DNA analysis of *COL1A1/2* (90%) and *non-COL1* (10%) gene in peripheral blood or cultured fibroblasts using next generation sequencing. Trans iliac bone biopsy with histomorphometric analysis helps to distinguish specific types. Management of OI involves multidisciplinary team including pediatrician, endocrinologist, orthopedic surgeon, dentist, geneticist, social worker, physiotherapist and occupational therapist. Cyclical intravenous bisphosphonates is recognized as mainstay of pharmacotherapy in children with moderate to severe OI (OI type II, ≥2 long bones fracture per year for 2 consecutive years, or ≥2 vertebral compression fractures) [8]. Oral bisphosphonates are used for mild OI with recurrent fractures. The bisphosphonate therapy decreases the fracture incidence, relieves chronic bone pain and fatigue, and thus helps improve mobility. Over time the orthopedic management has been revolutionized with the use of telescoping intramedullary rods that extend with growth and provide protection from repeated fractures and deformity. Recombinant Growth Hormone in combination with bisphosphonates improves bone mineral density and growth velocity in prepubertal children with OI [9]. The rationale of gene therapy in OI is promising but still in experimental stage.

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