Advances in the Orthopedic Management of Osteogenesis Imperfecta

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KEYWORDS

• Osteogenesis imperfecta • Advances • Medical • Surgical • Orthopedic • Bisphosphonates • Intramedullary fixation

KEY POINTS

- Osteogenesis imperfecta (OI) can be a debilitating disease with a wide range of phenotypic manifestations.
- The Sillence subtypes of OI can be explained by different variations in genetic mutations.
- Bisphosphonate therapy augments bone turnover and increases bone density in OI patients, although its efficacy in preventing fracture, reducing pain, and improving function is controversial.
- Recommendations for indications, duration, and type of bisphosphonate therapy in children have not been agreed upon.
- Fassier-Duval rodding systems show great promise in decreasing fracture rates while requiring less revision and causing fewer complications traditionally seen with older systems.

THE SCIENCE AND GENETICS OF OSTEOGENESIS IMPERFECTA

History

The first scientific documentation of osteogenesis imperfecta (OI) by army surgeon Olaus Jacob Elkman dates back to 1788. He detailed observational reports of bone fragility and fractures in 3 familial generations afflicted with "congenital osteomalacia."[1,2] OI was later given its name by Dutch professor Willem Vrolik in 1849.[3] The varying array of clinical manifestations grouped under this broad diagnosis sparked a field of study that aimed to classify and determine the root cause of this debilitating disease (**Fig. 1**). David Sillence developed his classification system in the 1970s, that has since been added to and modified, but is still widely used today (**Table 1**).[4]

Past Discovery

Electron microscopy research in OI patients in the 1970s led to the discovery of altered collagen structure in these patients compared with that of normal histologic controls.[5] This collagen was branded Type I, as it was the first discovery of altered connective tissue leading to clinical disease. In the 1980s, a gene deletion coding for the pro-α1 collagen chain steered the discovery of poor collagen synthesis and inspired further research detailing the underlying genetic causes of OI.[6,7] As a result, it was thought for a long time that mutations in collagen type I genes (COLA1 or COLA2) were the sole cause of OI, and that it was an autosomal dominant disorder.

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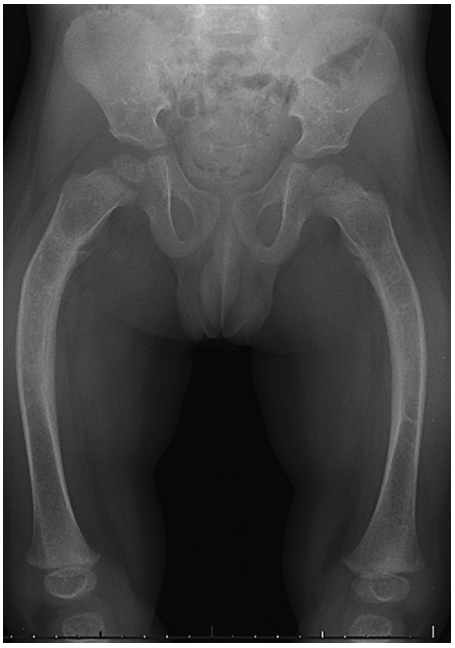

Fig. 1. Anteroposterior (AP) radiograph of a 2-year-old male infant with OI, with bowing deformity of the bilateral femurs and a history of multiple prior femur fractures.

Table 1
Types of osteogenesis imperfecta (OI), gene defect, and inheritance

OI Type	Gene Defect	Inheritance
I	COLA1	AD
II	COLA1/COLA2	AD
III	COLA1/COLA2	AD
IV	COLA1/COLA2	AD
V	Not known	AR
VI	SERPINF1	AR
VII	CRTAP	AR
VIII	LEPRE1	AR
IX	PPIB	AR
X	SERPINH1	AR
XI	FKB910	AR
N/A	PLOD2	AR
N/A	LRP5	AR
N/A	SP7	AR

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; N/A, not yet classified.

Data from Morello R, Esposito PW. Osteogenesis imperfect. In: Lin Y, editor. Osteogenesis. Rijeka (Croatia):InTech; 2012. Chapter 9:223–52.

Current Genetics

In the early 1990s, Wallis and colleagues[8] described cases of OI not caused by mutations in COLA1 or COLA2. Stemming from this study, there has been the discovery of multiple new forms of OI not originally described by Sillence. These forms involve various other genetic defects that manifest in an autosomal-recessive fashion. These genetic defects involve CRTAP,[9] LEPRE1,[10] PPIB,[11] SERPINH1,[12] SERPINF1,[13] PLOD2,[14] FKBP10,[15] LRP5,[16] and SP7[17] (see **Table 1**).

DIAGNOSIS OF OI

Prenatal

Our understanding of this disease from a genetic level has not only allowed for more accurate diagnosis of the disease using collagen molecular testing,[18] but also has allowed us to understand the manifestations of the disease, even as early as the prenatal period.[19] Features that can be seen on prenatal ultrasonography usually between 14 and 18 weeks of gestation (for Types II and III OI; Type I cannot be easily diagnosed) include increased nuchal translucency,[20] reduced echogenicity of bones,[21] multiple fractures of the long bones, ribs, and skull at various stages of healing,[21] and bowing of the long bones (+/− shortening).[22] Once there is a concern for OI via prenatal ultrasonography, the diagnosis can be made via either (1) chorionic villus sampling demonstrating abnormal type I collagen via electrophoresis, or (2) amniocentesis, which obtains fetal DNA for molecular analysis.[18] As the majority of mutations will involve COLA1/COLA2 genes, testing is centered around the identification of these genes followed by examination of the other aforementioned genes.

Postnatal

In the postnatal period, positive clinical findings (multiple fractures, blue sclera, and so forth) and the exclusion of other metabolic causes of osteoporosis can then warrant confirmation of the diagnosis via dermal biopsy and/or DNA analysis. Dermal biopsy has been shown to be about 90% positive in suspected OI cases,[23] whereas DNA analysis has been able to identify COLA1/COLA2 mutations in 95% of cases of OI, with the remaining percentage having CRTAP/LEPRE1 mutations.[9,24] As a result, it may be suggested that DNA testing should be utilized because it is more sensitive for disease diagnosis. Best-practice guidelines exist for the laboratory diagnosis of OI.[18]

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