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Osteogenesis imperfecta: clinical presentation, classification and treatment

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SUMMARY

Osteogenesis imperfecta is a bone disorder characterized by increased bone fragility, decreased bone mass between others. It depends mostly on the prevalence of gene mutations which altered the structural architecture of collagen type I. Many classifications have been published focusing on altered genes and severity of clinical features, but the one published by Sillence in 1979 and reviewed in 2010 and 2015 is the most widely accepted. The main goal of treatment in patients with OI is to achieve improvement in rate of mineral bone density, increase mobility, diminish fracture rate, self care and functional independece associated with a high quality of life.
Evidence level: V

Key words: Osteogenesis imperfecta, classification.
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RESUMEN

La osteogénesis imperfecta es un trastorno óseo caracterizado por un aumento de la fragilidad ósea, disminución de la masa ósea entre otros. Depende principalmente de la prevalencia de mutaciones genéticas que alteran la arquitectura estructural del colágeno tipo I. Se han publicado muchas clasificaciones centradas en los genes alterados y la gravedad de las características clínicas, pero la publicada por Sillence en 1979 y revisada en 2010 y 2015 es la más ampliamente aceptada. El objetivo principal del tratamiento en pacientes con OI es lograr una mejora en la tasa de densidad ósea mineral, aumentar la movilidad, disminuir la tasa de fracturas, el autocuidado y la independencia funcional asociada con una alta calidad de vida.
Nivel de evidencia: V

Palabras clave: Osteogénesis imperfecta, clasificación.
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INTRODUCTION

Osteogenesis imperfecta (OI), is a rare hereditary bone disorder characterized by increased bone fragility, decreased bone mass, short stature, bone pain, long bone deformities, low muscle mass, joint hypermobility and in some cases persistence of blue sclera, early hearing impairmaint and valvular or cardiac failure.[12] It's incidence varies from 1:10,000-25,000 worldwide and it depends mostly on the prevalence of gene mutations which altered the structural architecture of collagen type I.[1-3] At the present time, more tan 1,000 autosomal mutations altering collagen have been implicated in the presence of OI.[4]

Collagen type I is a triple helix with two alpha-1 and one alpha-2 chains enconded by COL1A1 and COL1A2 genes. After translation has been done, proalpha chains are translocated in the rough endoplasmic reticulum and then folded into a triple helix under control of CRTAP, LEPRE 1, PPIB and FKBP10 genes. Moreover, it is modified to procollagen by the Golgi apparatus by stimuli of SERPINH1, PLOD2 and FKB10 genes, and finally delivered into the extracelular matrix by exocytosis where a removal of propeptides N and C will result in the formation of collagen,[5] so if any of these genes suffered deletion, disruption or deterioration OI may be evident.

Because there is significant variability in the clinical features and severity of OI, a classification had to be made based on shared characteristics, signs, symptoms and possible outcomes. Sillence, published the first description for OI in 1979 which was devided into four main groups (from mild to severe or lethal) focused on specific genetic inheritance, based on different specific phenotypes. After that classification, many others have been more focused on gene mutations, making them difficult to use and with no

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prognosis. So, recently in 2010 the Nosology Group of International Skeletal Dysplasia Society, decided to use the Sillence classification as the universal way to classify the degree of severity in OI, and in 2015 a new group was added to the classification. This OI type 5 group is radiologically phenotypically distinguishable from types 1 to 4 and it consideres all intra-oseous membrane ossifications.[6]

CLINICAL FINDINGS IN OI

The clinical presentation in OI could be divided into primary and associated features. In the primary, liability to fractures and osteoporosis is the main feature and it could be presented as much as sporadic fractures during childhood to multiple and lethal intrauterine fractures, depending on the type of OI.[7]

There is a wide variability in associated features depending on the type of OI, which may vary from distinct blueness of the sclerae in some patients, hearing impairment, secondary to conductive and sensorineural deficits,[8] short stature (specially children with types 3 and 4 OI fall of normal growth curves by one year of age, entering a plateau phase with flat or slow growth that last until age 4-5 years)[9] progressive skeletal deformity, including scoliosis and basilar impression, dentinogenesis imperfecta, joint hypermobility and in some cases cardiopulmonary dysfunction, such as valvular deterioration, multiple pneumonias, vertebral collapse and kyphoscoliosis which contributes to restrictive lung disease evolving into a progressive *cor pulmonale*. All of this cardiopulmonary diseases are the major cause of mortality directly related to the disorder.[10]

CLASSIFICATION

The reviewed classification of Sillence in 2015 stated the pathology in 5 different types of OI which now are enumerated by arabic numbers (instead of Roman numbers).

OI type 1: non deforming OI with blue sclerae. This type of osteogenesis is characterized by low bone mass associated with increased bone fragility. In some cases hearing impairment is also present. blue sclerae is determinant in this group of OI. Scoliosis, Kyphoscoliosis and limb deformities are not common.[11]

OI type 2: extremely severe features including multiple intrauterine fractures that can be detected by fetus ultrasound at 18-20 weeks gestation. It can be seen deformities of long bones, marked deficiency of ossification in facial and skull bones, rib fractures. Almost all babies dies before the first month of age.[12]

OI type 3: progressively deforming group. Characterized by increased bone fragility and multiple fractures during childhood with progressive deformity of the skeleton. White sclerae is normally seen on this patients. All patients have poor longitudinal growth and fall well below the third centile in height for age and sex. Scoliosis begins at early age and increases over time.[13]

OI type 4: these group is characterized by multiple fractures, low bone mass, ocasionally low-middle deformity in long bones, dentinogenesis imperfecta and always having White-gray sclerae.[14]

OI type 5: patients of these group always have forearm and lower limb calcification of the inter-osseous membrane associated to low/moderate rate of fractures. No dentinogenesis imperfecta is seen on these group.[15]

TREATMENT

A multidisciplinary approach is necessary for the clinical management of patients with OI. The main goal of treatment is to achieve improvement in mobility, diminish fracture rate, self care and functional independece associated with a high quality of life. It is necessary a drug therapy to promote bone remodelling, to rise bone mass and to dimish bone fracture. A good Surgical or conservative treatment for stabilisation of fractures is important to avoid pain and bone deformity. After medical and/or surgical treatment, physical therapy is mandatory for muscular strengthening and alone or assisted walking strategy.[16]

Talking about drug therapy, bisphosponates are one of the major pharmacotherapeutic agents clinically prescribed for OI. These agents supress bone remodeling and inhibit calcification by inactivating osteoclasts which in turn decreases areal bone mineral density primarily in the spine, hip and femur and diminish fracture rates.[17] Some medical reports mentioned that growth hormone (despite patients with OI are not typically associated with growth hormone deficiency) can be beneficiated by increasing areal bone mineral density thus growth velocity in children with OI.[18]

Newly medical therapy, as teriparatide (a bone stimulating recombinant form of parathyroid hormone used to treate osteoporosis) has shown good results in improving bone mineral density, accelerate the healing of fractures and decrease bone fracture rates.[19]

Fracture management can be done surgical or conservative but the main goal is to achive a good stabilization and alignement to avoid progressive deformities. Prophylactic correction of deformity with intramedullary rods reduce importantly the risk of future fractures.[20] Spine deformity, listhesis and spondylosis are common problems in patients with OI at early ages. So muscular strengthening, low impact excercise and bracing would be beneficial for these patients to avoid back pain, and deformities of higher and lower spine.[21]

Cardiopulmonary therapy should be given to these patients to diminish the incidence of cor pulmonale and its proper complications which by far are the main source of mortallity in OI patients.

CONCLUSIONS

OI is a rare medical condition associated to extremely incapacitant features which may need to be treated by a multidisciplinary approach. The main goal in the treatment of these group of patients is to improve quality of life, increase mobility and decrease fractures rates. All of these may only be achieved if the medical doctors understand the pathophysiology of these desease and work in conjunction for the benefit of the patient.

References

1. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. *Nat Rev Endocrinol*. 2011; 7(9): 540-557.
2. Radunovic Z, Wekre LL, Diep LM, Steine K. Cardiovascular abonarmilities in adults with osteogenesis imperfecta. *Am Heart J*. 2011; 161(3): 523-529.
3. Steiner RD, Adsit J, Basel D. COL1A1/2-Related osteogenesis imperfecta.
4. Chu ML, Williams CJ, Pepe G, Hirsch JL, Prockop DJ, Ramirez F. Internal deletion in a collagen gene in a perinatal lethal form of osteogenesis imperfecta. *Nature*. 1983; 304(5921): 78-80.
5. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet*. 2004; 363(9418): 1377-1385.
6. 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*. 2011; 155(5): 943-968.
7. Sillence DO. Bone dysplasia. *Genetic and ultrastructural aspects with reference to osteogenesis imperfecta*. Ann Arbor, Michigan University Microfilms. 1980.
8. Garretsen AJ, Cremers CW, Huygén PL. Hearing loss in relation to age in osteogenesis imperfecta type I. Ann Otol Rhinol Laryngol. 1997; 106(7 Pt 1): 575-582.
9. Marini JC, Bordenick S, Heavner G, Rose S, Chrousos GP. Evaluation of growth hormone axis and responsiveness to growth stimulation of short children with Osteogenesis imperfecta. *Am J Med Genet*. 1993; 45(2): 261-264.
10. Bailleul-Forestier I, Berdal A, Vinckier F, de Ravel T, Fryns JP, Verloes A. The genetic basis of inherited anomalies of the teeth. Part 2: Syndromes with significant dental development. *Eur J Med Genet*. 2008; 51(5): 383-408.
11. Vetter U, Pontz B, Zauner E, Brenner RE, Spranger J. Osteogenesis imperfecta: a clinical study of the first ten years of life. *Calcif Tissue Int*. 1992; 50(1): 36-41.
12. Sillence DO, Barlow KK, Garber AP, Hall JG, Rimoin DL. Osteogenesis imperfecta type II delineation of the phenotype with reference to genetic heterogeneity. *Am J Med Genet*. 1984; 17(2): 407-423.
13. Byers PH, Pyott SM. Recessively inherited forms of osteogenesis imperfecta. *Annu Rev Genet*. 2012; 46: 475-497.
14. Van Dijk FS, Pals G, Van Rijn RR, Nikkels PG, Cobben JM. Classification of osteogenesis imperfecta revisited. *Eur J Med Genet*. 2010; 53(1): 1-5.
15. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Gen Part A*. 2014; 164A(6): 1470-1481.
16. Montpetit K, Palomo T, Glorieux FH, Fassier F, Rauch F. Multidisciplinary treatment of severe osteogenesis imperfecta: functional outcomes at skeletal maturity. *Arch Phys Med Rehabil*. 2015; 96(10): 1834-1839.
17. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosponate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev*. 2014; (7): CD005088.
18. Antoniazzi F, Monti E, Venturi G, Franceschi R, Doro F, Gatti D et al. GH in combination with bisphosponate treatment in osteogenesis imperfecta. *Eur J Endocrinol*. 2010; 163(3): 479-487.
19. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone for 2 years and relevance to human safety. *Toxicol Pathol*. 2002; 30(3): 312-321.
20. El-Adl G, Khalil MA, Enan A, Mostafa MF, El-Lakkany MR. Telescoping versus non-telescoping rods in the treatment of osteogenesis imperfecta. *Acta Orthop Belg.* 2009; 75(2): 200-208.
21. Arundel P. Osteogenesis imperfecta. *Paediatr Child Health*. 2015; 25(12): 574-579.

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