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Case Study

Osteogenesis Imperfecta due to Frameshift Mutation of the Col1a1 Gene

Adriana Sarit Lambraño A[1,3], Valentina Mejia[2] and Liliana Mejía de Beldjenna[1,3]*

[1]*Resident of pediatrics , Department of Pediatrics, Universidad Libre - Seccional Cali, Colombia*

[2]*Medical Student, University of Buenos Aires, Buenos Aires, Argentina*

[3]*Endocrinology pediatrics Children's Clinic Fundation Club Noel Cali Colombia*

[1,3]*Pediatrics Research Group GRINPED COL, Colombia*

***Corresponding Author:** Liliana Mejía de Beldjenna, Pediatric Endocrinologist, Children's Clinic Fundation Club Noel Cali, Department of Pediatrics, Universidad Libre - Seccional Cali, Colombia.

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Abstract

Osteogenesis imperfecta (OI), considered an orphan disease, is characterized by mutations in the genes that encode collagen proteins, especially type I. It is manifested by skeletal and extra skeletal clinical manifestations and in some cases it can present from the prenatal stage with severe compromise, which requires early diagnosis to provide timely and targeted treatment to reduce the morbidity and mortality of this pathology. We describe the clinical case of a patient with genetic confirmation of osteogenesis imperfecta carrying a rare mutation in the COLA1 gene.

Keywords: *Osteogenesis; Bisphosphonates; Genetics; Rare Diseases; Collagen*

Abbreviations

OI: Imperfect Osteogenesis; AR: Autosomal Recessive; AD: Autosomal Dominant

Introduction

Osteogenesis imperfecta (OI) encompasses a group of genetic disorders characterized by altered connective tissue formation, mainly type 1, which confers increased bone fragility and risk of fractures. It is also called "brittle bone disease". It is considered an orphan disease. Its incidence is estimated between 1/15,000 and 1/20,000 newborns and affects both sexes, races and ethnic groups equally. It comprises a wide spectrum of phenotypic presentations ranging from mild forms with few fractures, progressive bone deformities to severe forms with intrauterine fractures and death in the neonatal period [1-3].

In 80 to 90% of cases it is caused by mutations of two genes encoding type 1 collagen chains; COL1A 1, located on chromosome 17 and COL1A 2, located on chromosome 7. The type of inheritance varies according to the types and subtypes of OI. In 90% of cases it corresponds to an autosomal dominant variant. Connective tissue involvement includes abnormalities in the structure, formation or quantity of collagen, post-transcriptional modifications in folding, intracellular transport or in its incorporation into the bone matrix [4,5].

Type 1 collagen fibers are a structural component of the extracellular matrix of connective tissue, contributing to the ductility and strength of bone, as opposed to stiffness and strength which are mainly provided by the mineral component. Type I collagen is initially produced as type I procollagen consisting of two proa1 and one proa2 chains, which are encoded by the COL1A1 and COL1A2 genes, respective.

Classification is based on clinical presentation and severity; however, specific types have been defined by characteristic clinical and histopathological findings or according to the location of the underlying mutations.

The clinical manifestations not only include fractures and bone deformities, but also include extra skeletal manifestations, such as involvement of the eyes, ears and, less frequently, oral and visual manifestations [1].

The diagnosis is clinical, however radiographs, transiliac bone biopsy and molecular studies contribute to confirm the diagnosis. Treatment includes physiotherapy, rehabilitation, orthopedic surgery and management with bisphosphonates, calcium and vitamin D [6].

Given the multisystemic involvement of this pathology, the affectation from its prenatal stage and the risk of morbimortality, a timely and adequate intervention should be made to all patients with clinical suspicion to improve their quality of life, decrease progression of deformities and complications.

Clinical Case

Female, 5 years 1 month old, referred to pediatric endocrinology for family history of grandfather and father with osteogenesis imperfecta confirmed by genetic panel, who have presented multiple fractures throughout their lives. No important personal history, no parental consanguinity, no fractures, physical examination in good general condition with short stature: weight 16.1 kg (P/E: SD -1) height 95 cm (T/E: SD -3 short stature) BMI 16.10 kg/m^2 (BMI/E: 1). There is evidence of dentinogenesis imperfecta, blue sclerae, without evident bone deformity. Normal bone metabolism profile. A panel of genes associated with this pathology was requested for diagnostic confirmation (Table 1).

Patient	Normal
Calcium 10.6 mg/dl	8.5 - 11 mg
PTH 16.9 pg/ml	10 - 55 pg/ml
Phosphorus 4.60 mg/dl	4.0 - 7.0 mg/dl
Alkaline phosphatase 263.0 UI/L	< 673 UI/L
Vit D 30.0 ng/ml	20 - 40 ng/ml

Table 1: *Laboratory findings.*

Result of the genetic study with variants compatible with Osteogenesis Imperfecta (Chromosome 7 and 17) COL1A1 and COL1A2 gene. Homozygous recessive SPLICE variant and another heterozygous variant COL A1 c.441 of the 2 FRAMESHIFT DM dominant variant also found in the father, together with another homozygous variant in COL1A2 c.937-3c>t and c.1645c>g.

Discussion

Osteogenesis imperfecta or also known “crystal bone disease” in a is a pathology of genetic cause with autosomal dominant, recessive or X-linked inheritance with variable clinical expressivity according to the affected gene [1], presenting an identifiable pathogenic variant in the COL1A1 and COL1A2 genes that encode the pro-collagen I peptide chains. These chains are formed by two peptide chains of pro-collagen α1 (encoded by COL1A1) and another of pro-collagen α2 (encoded by COL1A2) in a triple helix. They present an amino acid sequence comprising a glycine (Gly) in combination with 2 other more variable amino acids: triplet Gly-X-Y where X is proline and Y is hydroxyproline [7].

Depending on the characteristics of the amino acid that replaces the glycine and the point in the chain at which the alteration occurs, a more or less severe form of OI may occur. Apart from glycine substitutions, other mutations can occur in OI: frameshift, split site, non-

sense.... The milder forms are characterized mainly because the mutation involved causes a premature stop co-donation to appear and the chain ceases to form properly, in this case less collagen is produced but it is functional, i.e. the defect is quantitative, in severe cases, abnormal procollagen chains are synthesized which when combined with normal procollagen chains give rise to a triple helix of collagen of abnormal structure and therefore to a production of collagen of poor quality leading to a qualitative defect [1].

In the case presented here there was a frameshift mutation of the COL1A1 gene and she had mild clinical manifestations.

Clinical features associated with osteogenesis imperfecta include: Triangular facies due to altered skull shape and evidence of multiple wormian bones on radiographic imaging. Ocular involvement most frequently blue sclerae that may occur in some patients, in addition they may have corneal alterations, refractive error and glaucoma, dentinogenesis imperfecta or (opalescent teeth) which is characterized by a yellowish discoloration of the teeth due to poor formation of dentin which is rich in collagen, The hypoacusis that is generated from the second decade of life tends to be mixed due to otosclerosis and ankylosis of the stapes. Skeletal manifestations include fractures, deformity of long bones secondary to fracture or to the same bony weakness with the typical incurvation of the femur in anterolateral direction and of the tibia in anterior direction called sabre tibia. Scoliosis may occur in up to 80% of patients with OI, and spondylolisthesis and spondylolisthesis in the lumbar spine more frequently, joint hyperextensibility favors dislocations and sprains, delayed motor development and secondary short stature. Some patients may present platybasia; and a rare but potentially serious complication, basilar invagination [3,4]. deformities at the hip level, in the form of coxa vara and less frequently coxa valga.

Patients with OI with type I collagen mutations can be classified into five clinically defined types according to their severity. Type I OI is the mildest form and may or may not present dentinogenesis imperfecta. Fractures may appear at the onset of ambulation and diminish after puberty. 50% present with deafness, which frequently appears in the second decade of life. Deafness is usually mixed, sensorineural and conduction deafness. Type II is lethal in the perinatal period. Intrauterine death may occur, during labor or weeks after birth due to respiratory failure and/or pneumonia, children are born with abducted hips and flexed knees and intrauterine fractures may occur. Type III OI is the intermediate form that progressively worsens with age, presenting an increase in the number of fractures, short stature and scoliosis, and also frequently presents with respiratory insufficiency, valvular insufficiency and cor pulmonale. Type IV is the moderate form, the diagnosis usually begins with ambulation, the sclerae are blue during infancy and white in adulthood. Patients have numerous fractures that decrease after puberty. They are usually short in stature and present platybasia and scoliosis. This form is compatible with a practically normal life and finally type V presents with the triad: dense metaphyseal bands, fractures with hypertrophic callus and calcification of the interosseous membrane of the forearm [1,3].

There is a classification based on genetic alterations that every day adds more types with the description of new mutations as described in table 2.

Type	Genetic defect	Heritage	Defective protein
I, II, III, IV	COL1A1 COL1A2	AD	Collagen α1 o o α2
V	IFITM5	AD	BRIL (o IFITM5)
VI	SERPINF1	AR	PEDF
VII	CRTAP	AR	CRTAP
VIII	P3H1 (LEPRE1)	AR	P3H1
IX	PPIB	AR	CyPB (o PPIB)
X	SERPINH1	AR	HSP47
XI	FKBP10	AR	FKBP65 (o FKBP10)

XII	BMP1	AR	BMP1
XIII	SP7	AR	OSTERIX
XIV	TMEM38B	AR	TRIC-B
XV	WNT1	AR (AD)	WNT1
XVI	CREB3L1	AR	OASIS
XVII	SPARC	AR	SPARC (o osteonectina)
XVIII	MBTPS2	Ligada X	Sp2

Table 2: *AR: Autosomal Recessive; AD: Autosomal Dominant.*

In the case of our patient her main clinical manifestations were blue sclerae, dentinogenesis imperfecta and short stature. She did not present long bone deformity and had no fractures and was classified as type I. Follow-up and nutritional support with calcium and vitamin D was provided.

Diagnosis is based on family history, physical characteristics and radiological findings, presence of fractures without major trauma or fractures at birth. Prenatal diagnosis of OI by ultrasound can be made by the presence of in utero fractures or suspected by asymmetric or disproportionate segments. Diagnostic confirmation should be made by molecular study that identifies the gene mutation associated with this pathology since it is useful to determine with certainty the type and to facilitate prenatal screening and diagnosis of the family and genetic counseling.

Treatment is multidisciplinary and includes physical rehabilitation, psychological, medical and surgical management [1].

Orthopedic management includes correction of bone deformity fractures with endomedullary nailing osteotomies, telescopic nailing that lengthens as the bone grows in length.

Pharmacological management is carried out with bisphosphonates, which are analogs of pyrophosphate that bind avidly to the hydroxyapatite crystals in the mineralized bone. They decrease the function and number of osteoclasts and thus inhibit bone resorption [6]. They also increase bone mineral density and reduce the risk of fracture in osteogenesis imperfecta [1]. The most commonly used in pediatrics due to the ease of application are zoledronic acid whose dose in 2 years is 0.05 mg/kg every 6 months and of the intravenous bisphosphonates, pamidronate at doses in 2 years a dose of 0.056 - 1.125 mg /kg for 2 - 3 days every 3 months; in both the first time of infusion should be half the dose. They should be applied in infusion or intensive care units to previously monitor calcium, phosphorus, vitamin D levels, renal function, avoiding hypocalcemia (secondary laryngospasm arrhythmias), hypophosphatemia and allergic reactions. The long-term adverse event in adults has been osteonecrosis of the jaw and of oral bisphosphonates is esophagitis.

Conclusion

OI is a genetic pathology with multisystemic manifestations and involvement. Our patient had a frameshift variant of the COL1A1 gene of autosomal dominant inheritance and presented with ocular and dental clinical manifestations associated with short stature without fractures or deformities.

OI involves ocular, auditory, oral and skeletal anomalies with multiple deformities and fractures; clinical manifestations may present prenatally or in childhood with a high morbidity and mortality burden. Hence the importance of making an early diagnosis in order to perform a timely and specific intervention, prevent complications and improve the quality of life of patients.

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Declaration of Conflict of Interest

None of the authors has a conflict of interest and the research is funded by the authors' own resources.

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