v. 3, n. 73, 2023

International Journal of Health Science

OSTEOGENESIS IMPERFECTA TYPE I REPORT OF TWO CASES

Magdalena Otazú
Endocrinology and Metabolism. Pereira Rossell Hospital
``Universidad de la republica``, Montevideo, Uruguay

Sofía Saccone
Endocrinology and Metabolism. Hospital Pereira Rossell
``Universidad de la republica``, Montevideo, Uruguay

Rosa Finozzi
Endocrinology and Metabolism. Hospital Pereira Rossell
``Universidad de la republica``, Montevideo, Uruguay

The authors declare not to have any interest conflicts.

Abstract: Osteogenesis imperfecta (OI) is a rare disease, genetically autosomal dominant; It is characterized by mutations in collagen-forming genes, with high bone fragility and risk of fractures. OI type I is the most common and mild form. 2 clinical cases of this entity are presented, evaluated at the Pereira Rossell Hospital, in the period 2020-2021. These are two girls, ages 2 and 4, with a clinical diagnosis of OI type I in the first months of life. The oldest has a genetic study, mutation of the Col1A1 gene. They share the presence of three fragility fractures in long bones, tibial bone deformities, hypermobility, and blue sclerae. The youngest is short and both have normal development. Phosphocalcium metabolism is normal and they are replaced with vitamin D3. The diagnosis of OI is clinical, radiological and genetic. The presentation The clinical picture is heterogeneous with skeletal manifestations, such as fractures, deformities and growth retardation; and extra-skeletal manifestations, such as bluish discoloration of the sclera, dentinogenesis imperfecta and hearing loss. Bone densitometry and radiography are the imaging studies of choice. A mutation in the Col1a1 and Col1a2 genes, which encode the α chains of type I collagen, is identified in 90% of cases. The objective of treatment is to improve quality of life through a multidisciplinary approach including physical rehabilitation, orthopedic surgery, pharmacological treatment with bisphosphonates, hearing management and dental anomalies.
Keywords: osteogenesis imperfecta, brittle bones, bisphosphonates.

INTRODUCTION

OI or "brittle bone disease" is an autosomal dominant genetic disease, characterized by alterations in collagen formation, with high bone fragility and risk of fractures [1,2]. *Four groups* are classically recognized, type I is the most frequent and mild form. Given its low incidence, 1/20,000 newborns, it belongs to rare disease group [3]. Below, 2 clinical cases of OI in girls are presented and a bibliographic search on the subject is carried out.

CLINICAL CASES

These are two girls, 2 and 4 years old, with no family or perinatal history of note. In the youngest girl, growth delay is notable, with a height below the 3rd percentile from 4 months, with a corresponding bone age. *Figure 1.* Regarding development, both meet the milestones for their age; and the nutritional history is adequate. Clinically and radiologically, they share the presence of fragility fractures. The youngest girl suffered a fracture of the left tibia at 6 months, a periorbital fracture at 10 months, a middiaphyseal fracture of the left femur at 16 months, and an oblique middiaphyseal fracture of the left tibia with low kinematics at 2 years. The older girl presented a fracture of a metatarsal in the right foot at one year of age and in the left distal tibia at 3 years of age. At the moment none require surgical treatment. Child abuse is ruled out. On the other hand, both present tibial bone deformities, hypermobility and blue sclerae. *Figure 2.* Additionally, the older girl has scoliosis and dentinogenesis imperfecta. *Figure 3.* Phosphocalcium metabolism is normal and Bone densitometry is pending.

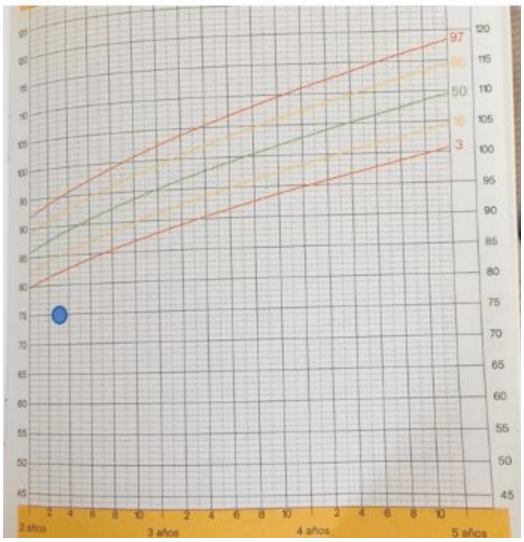


Figure 1. Height percentiles according to age. Growth is observed below the 3rd percentile.

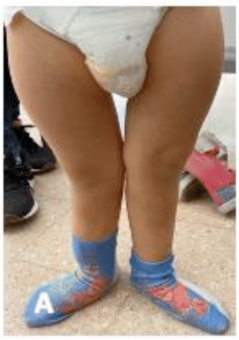
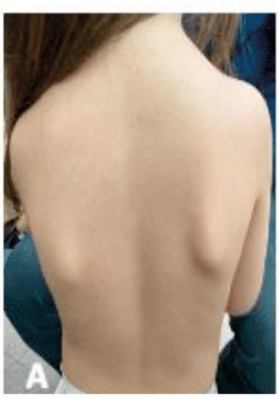


Figure 2. A. Tibial bone deformities.

B. Blue sclerae



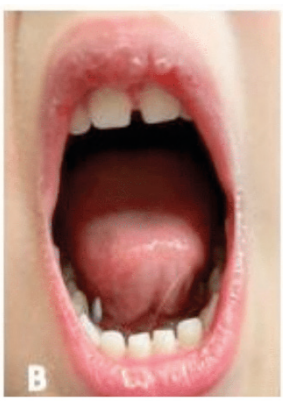


Figure 3. A. Scoliosis.

B. Imperfect Dentinogenesis

A clinical diagnosis of OI type I was made in both girls. In the older one, there is a genetic study with confirmation of the Col1A1 gene mutation.

The goal of treatment is to improve your quality of life through a multidisciplinary approach to the possible conditions associated with the disease.

They are replaced with vitamin D3 and are being monitored by endocrinology, traumatology, genetics and physiatry teams. Evaluation by otorhinology, ophthalmology, dentistry, psychology and social worker is pending. Another fundamental pillar is pharmacological treatment with bisphosphonates to improve bone mineral density, and thus prevent new fractures. In conjunction with traumatology, it was decided to assess the opportunity to start intravenous pamidronate.

DISCUSSION

OI is a syndrome that includes a set of diseases caused by a heterogeneous and hereditary disorder of the connective tissue; It mainly affects the production of type 1 collagen. This protein, the most abundant in bone, tendons and skin, is synthesized in the endoplasmic reticulum after the assembly of two procollagen α1 and α2 peptide chains, encoded by Col1A1 and Col1A2 respectively. In 90% of cases it is caused by autosomal dominant or de novo heterozygous mutations in one of these genes[1]. Different types and classifications of OI have been described, the most classic being Sillence. 4 types are described according to the genetic basis and clinical characteristics. *Figure 4*. OI type I corresponds to the most frequent type, it is mild in intensity, and according to the existence or not of dentinogenesis imperfecta it is subdivided into A and B. Some cases of OI do not fit within the four classic categories, so Two types have been added, with the particularity

of not presenting mutations in the collagen I genes [3,4]. The diagnosis is made through an adequate history, physical examination, radiological findings and confirmation by genetic and/or biochemical study [2,5]. The clinical presentation is variable, with skeletal manifestations, such as fractures due to mild trauma, deformities in long bones, scoliosis and growth retardation; and extra-skeletal manifestations, such as bluish discoloration of the sclera, dentinogenesis imperfecta and hearing loss [6]. Less frequently, some patients may also present manifestations at the cardio-pulmonary level [7]. In a study carried out in Holguín by Torres Molina et al. On a clinical case of an infant, reference is made to the main clinical characteristics of the different types of OI. Type I is generally expressed late and the classic Van der Hoever triad is observed, manifesting with bone fragility, blue sclerae and deafness [8]. Fractures and bone deformity occur mainly in childhood, but the risk fracture rate remains high in adulthood [2,6]. Cases of OI type I present fractures at birth in only 8% of cases; up to 23% in the first year of life, 45% in preschool age, and 17% in school age [9].

Bone densitometry and radiography are the imaging studies of choice. The lumbar spine and femoral neck are assessed. Many studies describe the difficulty in analyzing densitometry results due to the considerable deformities that patients present. Furthermore, they frequently present scoliosis (39-80%), which also makes evaluation difficult [6].

Generally, biochemical parameters of bone metabolism are usually normal in OI. Elevation of alkaline phosphatase, hypercalciuria, low bone formation markers and elevated bone resorption markers can guide the diagnosis, mainly in severely affected subjects [1].

It is worth highlighting that it is necessary to carry out a differential diagnosis with other pathologies, such as congenital hypophosphatemia, achondroplasia, juvenile idiopathic osteoporosis, among others [2,9].

Due to its clinical diversity, the management of OI must be multidisciplinary and adapted depending on the degree of bone involvement and fragility. It includes physical rehabilitation, orthopedic surgery, pharmacological treatment with bisphosphonates (BP), hearing management and dental anomalies [7].

Regarding pharmacological treatment, BPs are synthetic analogues of pyrophosphate that bind to bone, inhibiting bone resorption, and increase bone mineral density [7]. They are drugs widely administered in children with OI. Positive effects have been observed in bone histology, including an increase in the number of trabeculae and cortical thickening, as well as an increase in vertebral Z scores in densitometry [3]. Candidates for BP therapy are patients with moderate to severe forms of OI, with a high rate of fractures (2/3 or more in a year), vertebral crushing or bone deformities. Most children with moderate or severe forms are likely to benefit. There is no evidence of the benefit of treatment in mild forms, unless they have significant spinal involvement. The presence of pain in itself is not an indication, nor is the finding of altered densitometry as the only problem [10]. Before administering bisphosphonates, it must be checked that the patient has adequate serum levels of calcium, vitamin D and creatinine. Although BPs are generally well tolerated, the appearance of a flu-like syndrome during the first infusion of an intravenous bisphosphonate is not uncommon. Hypocalcemia is another relatively common adverse effect, so it is recommended to increase calcium intake during treatment with BF [7]. Most studies in OI are based on the use of intravenous pamidronate. Another option is zoledronate, the benefit of which is a single dose. Oral treatment with daily or weekly alendronate can be considered in mild forms [7,11]. *Figure 5.* The use of BP in patients with severe OI, who have short stature and marked bone

	TYPE I	TYPE II	TYPE III	TYPE IV	TYPE V	TYPE VI
Inheritance	AD	AD	AD	AD	AD	Uncertain
Associated mutations	Premature stop codon in COL1A1	Glycine substitutions in COL1A1 or COL1A2	Glycine substitutions in COL1A1 OR COL1A1 and COL1A2	Glycine substitutions in COL1A1 and COL1A2	are unknown	are unknown
Severity	Mild	Lethal	Serious	Half	Moderate	Half
Fractures	Few to multiple	Multiple	Serious even costal	Multiple	Multiple	Multiple
Bone deformities	rare	Severe	Variable Severe scoliosis	Moderate. Moderate-mild scoliosis	Moderate Hypertrophic calluses	Moderate to severe Scoliosis
Height	Normal or slightly low	Low	Very low triangular facies	slightly low	Mild to moderate loss	Slightly low
Dentinogenesis	Strange	Yes	Yes	50%	No	No
Sclera	Blue	Dark blue	White to grayish	Gray or white	Normal	Normal
Deafness	50%		<50%	100%	No	No

Figure 4. Extended Sillence classification.

Extracted from: Gutiérrez. M, Molina. A, Prieto. L, Parra. J. Osteogenesis imperfecta: new perspectives. Getafe University Hospital. Madrid. 2013.

Bisphosphonate	Administration	Most used doses and guidelines
Pamidronate	Intravenous	<2 years: 0.37-0.75 mg/kg for 2-3 days every 2 months 2-3 years: 0.56-1.125 mg/kg for 2-3 days every 3 months > 3 years: 0.75-1.5 mg/kg for 2-3 days every 4 months 1st infusion at half dose
Zoledronate	Intravenous	<2 years: 0.025 mg/kg every 3 months >2 years: 0.05 mg/kg every 6 months *1st infusion at half dose
Alendronate	Oral	<40 kg: 5 mg/day or 35 mg/week >40 kg: 10 mg/day or 70 mg/week

Figure 5. Dosage of bisphosphonates used for osteogenesis imperfecta.

Extracted from: Torrent RB. Imperfect osteogenesis. Sant Joan de Déu Hospital. Esplugues de Llobregat. Barcelona. 2020;349–59.

deformity, is described in the literature. The use of intermittent intravenous pamindronate was shown to decrease bone resorption, increase bone mineral density, and reduce the fracture rate; In addition, a dramatic effect on well-being and reduction in bone pain, which stimulated ambulation, was documented. However, more studies are needed to monitor the long-term effects of these drugs [12,13.] Studies in children have shown that benefits are greatest in the first 2 to 4 years of treatment [11,14.] Once densitometry improves above -2 standard deviations, it is recommended to reduce the dose and administration time; a 50% reduction in the annual dose is suggested. Discontinuation is not recommended in patients with severe OI 10.

In a retrospective study by Diaz et al, describing 15 cases of OI diagnosed between 2005 and 2017 in a Hospital in Spain, all patients had received bisphosphonates, but those who presented new fractures despite BP were started with teriparatide [6] Studies with teriparatide are giving encouraging results for patients with OI, although it appears that the

response varies depending on the type of OI. There are some data published with the anti-RANKL monoclonal antibody denosumab that may constitute a useful new therapy for these patients [3,15,16,17].

CONCLUSIONS

OI type I is a rare disease, autosomal dominant genetics, product of mutations in collagen-forming genes, and heterogeneous in its clinical presentation. The diagnosis is clinical, radiological and genetic. Bone densitometry and radiography are the imaging studies of choice. Most cases carry mutations in the COL1A1 and COL1A2 genes, the main protein of the extracellular matrix of bone tissue, skin and tendons.

The goal of treatment is to improve quality of life through a multidisciplinary approach.

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