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Case Report

Type I osteogenesis imperfecta: a case report

Osteogénesis imperfecta tipo I: reporte de caso

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RESUMEN

El término osteogénesis imperfecta incluye varios defectos genéticos del colágeno tipo 1 traducidos clínicamente en deformidad y fragilidad ósea. El tipo I o variante de Lobstein es la forma más frecuente de la enfermedad y se caracteriza por un patrón de herencia autosómico dominante.

Se reporta el caso de una paciente de 65 años de edad que acude a nuestro servicio en el Hospital "Lucía Íñiguez Landín" de Holguín, Cuba, con cuadro de fracturas múltiples luego de caída leve. La paciente presentaba un historial de múltiples fracturas a lo largo de su vida, hiperlaxitud articular, talla baja, coloración azul grisáceo de conjuntivas bulbares. Teniendo en cuenta los antecedentes familiares positivos y la evaluación fenotípica del cuadro, la paciente se diagnosticó con osteogénesis imperfecta tipo I. Una evaluación pormenorizada fue realizada y se administró la medicación disponible. La actualización diagnóstico-terapéutica de esta enfermedad en Cuba es fundamental para el mejoramiento de la calidad de vida de los afectados.

Palabras clave: osteogénesis imperfecta, fragilidad y deformidad ósea, fracturas múltiples, reporte de caso, actualización diagnóstico-terapéutica

ABSTRACT

The term osteogenesis imperfecta includes several genetic defects of type I collagen, clinically traduced in bone fragility and deformity. The type I or Lobstein variety is the most frequent form of the disease and is characterized by a pattern of autosomal dominant inheritance. The case of a 65-year-old female patient, who came to our medical service at "Lucia Iñiguez Landin" Hospital of Holguin, Cuba, with multiple fractures after a slight fall was reported. She had short stature, a history of multiple fractures along her life, joint hypermobility, and blue grayish bulbar conjunctiva. Given the positive family history and the phenotypic assessment of the clinical picture, the patient was diagnosed with type I osteogenesis imperfecta. A detailed evaluation was carried out and the available medication was prescribed. The diagnostic and therapeutic update on this disease in Cuba is crucial for enhancing life quality of those who are affected.

Keywords: osteogenesis imperfecta, bone fragility and deformity, multiple fractures, diagnostic and therapeutic update

Introduction

The term osteogenesis imperfecta (OI), also known as *Dighton-Adair* syndrome, was originally used to describe a group of connective tissue disorders characterized by bone fragility beginning from early childhood. In the modern era of advanced genetic studies, the OI term includes various quantitative and qualitative defects of type 1 collagen and non-collagenous matrix proteins, leading to decreased production and/or defective processing of type 1 collagen, eventually leading to impaired bone strength.[(1)] OI is a rare autosomal dominant metabolic bone disorder estimated to affect about 1/13 500–15 000 births, without including less severe forms recognized later in life.[(2)]

Considering genetics, genes involved includes not only *COL1A1* and *COL1A2*, but also a battery of genes encoding proteins involved in the proper folding of the triple helix of collagen. This generalized connective tissue disorder has major manifestations in bone, leading to skeletal fragility and substantial growth deficiency.

On clinical grounds, the diagnosis of OI is suspected in cases of bone fragility beginning in childhood associated with bone deformity.[(3)]

For OI clinical classification the *Sillence* scale, based on the clinical phenotype and the inheritance pattern, is still widely used, with type I also known as *Lobstein* form being the less severe, with autosomal dominant inheritance pattern, slight severity and blue/gray sclerae; type II, the most severe form, with recessive autosomal pattern, generally lethal at birth; type III, a severe form with recessive autosomal transmission and progressive deformity, and type IV, of moderated severity, normal sclerae and autosomal dominant inheritance.[(4)]

Despite current both diagnosis and therapeutic advances, OI remains as a cureless chronic disease; therefore it is paramount to define treatment goals considering age brackets in order to prevent or decrease complications and to avoid long term pharmacologic treatment associated side effects.[(5)] In Cuba, OI case reports are limited. [(6, 7, 8)] However, it might be associated to a sub-diagnosis of the disease, as occurred in the case here presented, where despite a long history of multiple fractures in the presence of suggestive clinical signs, the patient had lived unaware of her bone´s fragility cause and therefore, lacking a proper prophylactic and therapeutic advisory.

Case Report

A 65- year-old white woman, who was a housewife, was brought by her relatives into our emergency service at the "Lucia Iñiguez Landin" Hospital of Holguin complaining of severe pain, deformity and tumefaction of her right wrist along with signs of increasing pain and inflammation in her right knee, after suffering a slight fall from her own feet while climbing stairs several hours before. She fell forward over her right knee and at the same time she leaned her right palm on the floor in hyperextension.

On her past medical history she referred suffering from Arterial Hypertension for 14 years, effectively treated with one captopril tablet (25 mg) every 8 hours and one hydrochlorothiazide tablet (10 mg) every day.

Besides she referred suffering from multiple fractures along her life, and joint hypermobility during her childhood and youth that stopped when she reached adulthood. On physical examination the patient presented blue gray colored sclerae (See figure 1).

Besides, a 3 cm long wound located in the ventral portion of the right wrist was observed, with irregular edges and small drops of fat. In addition, a moderate swollen area with ecchymosis, functional impotence, intense pain and acquired deformity was observed in both her right wrist and knee due to the trauma. All peripheral pulses were present. The patient showed a short stature: 143 cm (4.6 feet). Weight: 42 kg. Body mass index within normal limits: 20.54 kg/m^2.

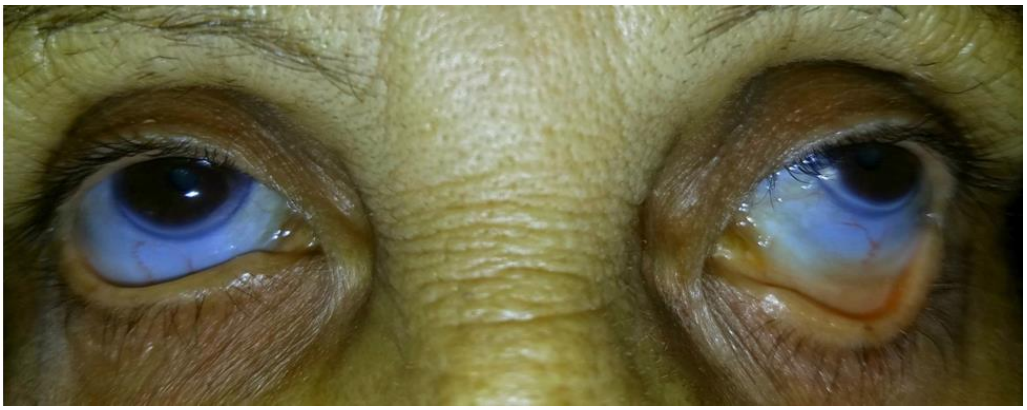

Figure 1: The picture shows the middle portion of the patient´s face, where we can observe the blue gray colored sclerae along with some signs of senile cataracts. The patient referred the color was more intense when she was young and that it has got lighter during adulthood.

Blood tests showed: Hemoglobin: 11.7 g/l; a negative blood type; glycaemia: 5.3 mmol/l, blood clotting: 1 second; platelet count: 190 x 10^9/l. Simple radiographies of right knee, wrist and

shoulder, pelvis and cranium in both anterior and lateral views were prescribed. Right wrist x-ray showed a transversal fracture in the distal third of both the radius and ulna, suggesting a complete exposed fracture of the right wrist. (See figure 2 *a, b*) Also, the lateral view of the right knee x-ray showed a complete transversal fracture of the patella. (See figure 2 *c, d*) An integral radiographic evaluation of the bone structures suggested a globally diminished bone mineral density index (BMDi).

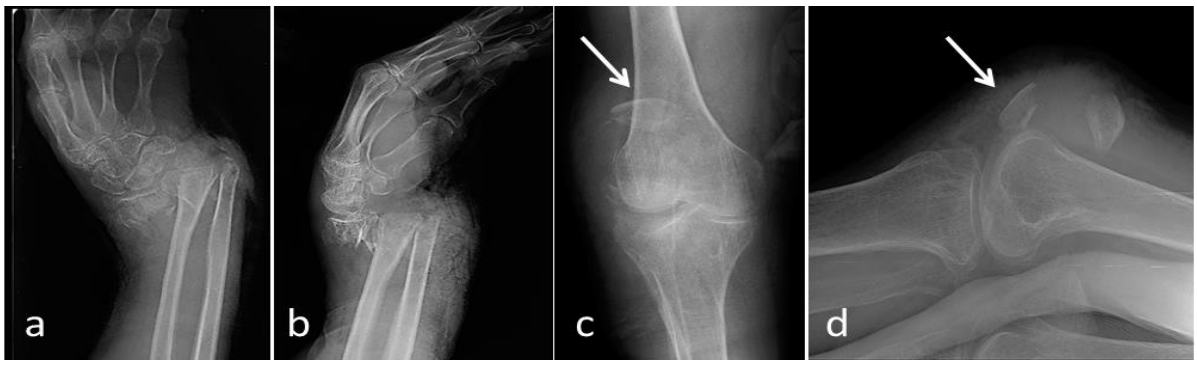

Figure 2: *a* shows a frontal view of the right wrist x-ray with a transversal fracture in the distal third of both the radius and ulna, suggesting a complete exposed fracture of the right wrist, with dorsal displacement of both fragments; b (lateral view) shows the distal ends of both the radius and the ulna fractured and completely displaced backwards; c shows a frontal view of the right knee x-ray with presence of a bone fragment displaced upwards; and *d* (lateral view) shows the presence of a complete transversal fracture of the patella, with displacement of the upper bone fragment.

Considering the severity of the lesions, after immobilization and parenteral hydration of the patient, urgent surgical treatment was indicated. Firstly bone reduction and osteosynthesis of the right wrist were performed, and then hemipatellectomy of the right knee was carried out. No complications were reported. As differential diagnosis the generalized severe osteoporosis and pathological fractures due to bone tumors were ruled out.

Considering the multiples previous fractures and the remote joint hyperextension history, a genetic cause was regarded. Interviewing also revealed that the patient´s mother also presented blue gray sclerae, and also the two patient´s daughters and her granddaughter. Furthermore, a daughter referred a multiple fractures history along her life. The information indicated a dominant pattern of transmission, causing blue gray colored sclerae and bone fragility. With these data, a presumptive diagnosis of type I OI was established. Finally, the patient was sent home, adding 1 tablet of metronidazole (250 mg) every 12 hours for 14 days,

one tablet of both folic acid (1 mg) and iron fumarate (200 mg) once day, and one tablet of vitamin D (25 mg) per day for three months, plus her regular treatment for blood pressure. No other therapeutic considerations were made.

Discussion

Osteogenesis imperfecta classifies among bone´s dysplasia due to alterations in bone´s density and modeling. Type I is the most frequent form of the disease and it is characterized by an autosomal dominant inheritance.[6] The clinical description of the disease is very wide, ranging from a lethal perinatal form to a moderated severity phenotype diagnosed lately in life, as in this case. Severe forms usually present at birth or immediately after labor, with severe bone fractures and deformities, while in the minor forms of the illness fractures tend to decrease in number along adulthood, reemerging after pregnancy or during menopause.[5]

In addition, there have been described several extra skeletal deformities including bowing of long bones, kyphoscoliosis, acetabular protrusion and chest wall deformities such as pectus excavatum or carinatum, barrel chest, joint hypermobility, anomalous formation of bone callus, hearing disorders and cardiovascular and neurological alterations, among others that need to be identify and treated.[5] From clinic grounds, OI type I diagnosis in the current case was made considering the multiple fractures history along the patient´s life, the presence of blue gray sclerae, her short stature and the joint hypermobility she referred.

The autosomal dominant pattern was established considering a positive family history of bone fractures and blue gray sclerae among the patient´s parents and descendants. Bone fragility in OI is complex and not entirely understood. Patients with OI tend to have low areal bone mineral density (ABMD), associated both with lower bone size and lower volumetric BMD, as shown in this case. Fractures involve vertebrae, ribs and upper and lower extremities, (as in our case); their rates vary significantly from less than one to several per year depending on the severity of the disease.

The prevalence of fractures in the mildest forms tends to be higher during childhood; then decreases after adolescence, although can reappears after menopause.[5] Our patient´s both eyes are blue gray colored, though she refers her sclerae color has lost intensity during adulthood. The presence of blue/gray sclerae is not uniform and might differ among patients

even within the same kindred. It is a feature of the OI type I, the mildest form, and the color of the sclerae can either stay stable over the years or might become less dark over time.[4]

It coincides with our patient´s description about her blue gray sclerae evolution. In addition; the patient referred a history of great joint hypermobility during her youth, accompanied by multiple fractures and joint dislocations. According to *Lindahl et al.* joint hypermobility is also a common feature and can be found in up to 66%–70% of patients with OI. Up to 56% of patients report a history of joint dislocation and up to 39% a history of tendon rupture.[1] However; joint hypermobility can decrease overtime along with the joints' range of motion and this is thought to be the effect of progressive stiffening associated with aging or with the mechanical effects of skeletal deformities and fractures. [9] The combination of fractures, deformities and low muscle strength leads to significant functional impairment with reduced ambulation. [1]

A requirement of the Lobstein form diagnosis is the presence of an autosomal dominant pattern.[4] The patient referred that her mother, her two daughters and her granddaughter also had blue gray sclerae and a multiple fractures history, suggesting a genetic disorder with vertical transmission. Around 90% of OI cases are caused by autosomal dominant mutations in the *COL1A1* or *COL1A2* genes, that either reduce the amount of type 1 collagen (quantitative defects) and present with a milder phenotype, or affect its structure (qualitative defects) and present with a more severe phenotype. [2]

The rest of the cases are caused by genetic defects in genes involved in the post-translational modification and intracellular trafficking of type 1 collagen or genes associated with osteoblasts differentiation and function. Those generally result in a moderate to severe phenotype.[5] It is interesting, however, that one of the patient´s daughter, still having blue gray sclerae, does not present a history of frequent fractures as her sister. It might be due to the wide genetic heterogeneity reported for OI, that can appear due to *de novo* mutations or due to both germinal and somatic mosaicisms.[2]

OI diagnosis in the Cuban population is supported in the genetic preconception risk detection programs that start in the primary care. However, many cases pass unnoticed and without the proper follow-up, and the diagnosis is finally made at an elderly age. Currently, OI prenatal diagnosis is based either on the analysis of fetal cells synthesized collagen, obtained by corionic biopsy during week 10 to 12 of pregnancy, or by studying *COL1A1* and *COL1A2* genes. Neither of these two studies are yet performed in our country.[6] Considering treatment, Cuba has a

wide range of strategies headed to prevent and rehabilitate injuries and disabilities provoked by skeletal illnesses. Nevertheless, regarding OI these strategies are still insufficient to provide an integral attention to the patients. Treatment goals include reduction of fracture incidence, management of bone pain, improvement of mobility, growth and independent leaving, detection and management of extra skeletal manifestations, and avoidance of short- and long-term adverse effects of drug treatment.[5]

Measures to improve bone health include nutrition, physical activity, and treatment of the underlying condition and associated comorbidities.[10] Currently bisphosphonates (BPs) such as alendronate, risedronate, pamidronate, zoledronate and neridronate, along with calcium and D vitamin supplements, represent the main pharmacological intervention in both pediatric and adult patients with OI, due to their positive effect over aBMD.[11] Anabolic therapy based on teriparatide, currently the only available anabolic agent, has shown promising results in adult patients with OI type I.[12] There are also a small number of clinical studies in adult patients with OI concerning denosumab, a monoclonal antibody targeting RANKL.[13] Neither of these pharmacological treatments are yet available for the Cuban population affected by OI.

Apart from pharmacological interventions, a multidisciplinary approach that includes experienced orthopedic surgeons, specialists in pediatric dental care, physiotherapists and occupational therapists is of outmost importance for delivering the best of care.[5] The improvement of these patients life quality demands an update of the Cuban diagnostic and therapeutic arsenal in order to provide an attention more effective and integral to OI patients.

Conclusion

OI is a genetic disorder of the bone metabolism clinically expressed as bone deformity and fragility, among many other extra skeletal manifestations. Its diagnosis is mainly both genetic and clinical. The clinical phenotype depends on the *Sillence* scale that includes four groups of patients. Type I or *Lobstein* syndrome is the most common and slight form.

Taking into account the multiple fractures history lifelong OI must be considered as a possible diagnosis, starting in the primary health care. Cuba develops a wide range of strategies to prevent and rehabilitate all kind of lesions and disabilities provoked by skeletal disease. However, an integral attention for this kind of patients is still not sufficient. A diagnostic and therapeutic upgrade of this illness in Cuba is paramount to increase the welfare of the Cuban patients affected by OI.

Bibliographic References

1. Lindahl K, Åström E, Rubin CJ, Grigelioniene G, Malmgren B, Ljunggren Ö, *et al*. Genetic epidemiology, prevalence, and genotype-phenotype correlations in the Swedish population with osteogenesis imperfecta. Eur J Hum Genet.2015[cited 19/12/2019]; 23(8):1042-1050. Available at: https://www.nature.com/articles/ejhg201581

2. Lim J, Grafe I, Alexander S, Lee B. Genetic causes and mechanisms of osteogenesis imperfecta. Bone 2017. [Cited 19/12/2019]; 102:40-49. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5607741/

3. Trejo P, Rauch F. Osteogenesis imperfecta in children and adolescents-new developments in diagnosis and treatment. Osteoporos Int. 2016[cited 25/01/2020]; 27(12):3427-3437.Available at: http://publicationslist.org/data/frauch/ref-315/Trejo-2016-Osteogenesis%20imperfecta%20in%20children.pdf

4. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979; [cited 25/01/2020]; 16(2):101-116. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1012733/

5. Tournis S, Dede A. Osteogenesis imperfect-A clinical update. Metabolismo 2018 [cited 26/01/2020];80:27-37. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0026049517301580

6. Hernández García I, Fernández Martín M, León Pérez S, García García A, Riaño Echenique J. Osteogénesis imperfecta: mosaicismo germinal o evidencia de heterogeneidad genética. Presentación de una familia y revisión bibliográfica. Rev Cubana Pediatr. 2007[cited

26/01/20];79(3). Available at: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0034-75312007000300012

7. García OA, Rives GY, Álvarez BD. Embarazada con Osteogénesis Imperfecta tipo IV. Revista Cubana de Obstetricia y Ginecología. 2019; [cited 28/1/2020]; 45(1):66-73. Available at: http://revginecobstetricia.sld.cu/index.php/gin/article/view/90

8. Torres Molina A. Huesos de cristal .Presentación de un caso. Medisur 2010[cited 28/01/20];8(4). Available at: http://medisur.sld.cu/index.php/medisur/article/view/1057

9. Uttarilli A, Shah H, SriLakshmi Bhavani G, Upadhyai P, Shukla A, Girisha KM. Phenotyping and genotyping of skeletal dysplasias: Evolution of a center and a decade of experience in India. Bone. 2019[cited 04/02/2020];120:204-211. Available at: https://www.sciencedirect.com/science/article/abs/pii/S875632821830406X

10. Gil JA, DeFroda SF, Sindhu K, Cruz AI, Daniels AH. Challenges of Fracture Management for Adults with Osteogenesis Imperfecta. Orthopedics. 2017[cited 25/08/2020];40(1):17-22. Available at: https://journals.healio.com/doi/abs/10.3928/01477447-20161006-04

11. Vuorimies I, Mäyränpää MK, Valta H, Kröger H, Toiviainen Salo S, Mäkitie O. Bisphosphonate Treatment and the Characteristics of Femoral Fractures in Children With Osteogenesis Imperfecta. J Clin Endocrinol Metab. 2017[cited 04/02/2020];102(4):1333-1339.Available at: https://academic.oup.com/jcem/article/102/4/1333/2913385

12. Nicol L, Wang Y, Smith R, Sloan J,Cs Nagamani S, Shapiro J, *et al.* Serum Sclerostin Levels in Adults With Osteogenesis Imperfecta: Comparison With Normal Individuals and Response to Teriparatide Therapy. J Bone Miner Res. 2018[cited 25/08/2020];33(2):307-315 . Available at: https://asbmr.onlinelibrary.wiley.com/doi/full/10.1002/jbmr.3312

13. Hoyer Kuhn H, Franklin J, Allo G, Kron M, Netzer C, Eysel P, *et al*. Safety and efficacy of denosumab in children with osteogenesis imperfect-a first prospective trial. J Musculoskelet Neuronal Interact.2016[cited 04/02/2020]16(1):24-32. Available at:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089451/

Sponsoring

None

Conflict of interests

The authors do not refer any conflict of interests.