Lusíadas Scientific Journal • VOL. 6 • #1 • janeiro/março 2025

# Osteogenesis Imperfecta Type III: Case Report and Comprehensive Analysis of Phenotypic Classification, Genetic Causes, and Therapeutic Approaches

## Osteogénese Imperfeita Tipo III: Relato de Caso e Análise Abrangente da Classificação Fenotípica, Causas Genéticas e Abordagens Terapêuticas

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https://doi.org/ 10.48687/lsj.220

## Abstract

Osteogenesis imperfecta (OI), known as brittle bone disease, is a genetic condition that affects the extracellular matrix of the skeletal system, causing bone fragility and potential impacts on other organs. Its prevalence varies from approximately 1 in 10 000 to 20 000 births and is associated with various genetic mutations. We report a case of a 14-month-old female patient diagnosed with OI type III, characterized by short stature, dental abnormalities, and bone fragility. Medical history includes effectively treating fevers, gastrointestinal, and respiratory issues. X-rays revealed fractures in bilateral femurs and humeri. She underwent femur surgery and continues to experience frequent fractures, unable to ambulate, under intensive medical care. OI is a genetic condition presenting with severe bone fragility, short stature, and progressive deformities, necessitating accurate diagnosis and effective treatment to improve quality of life.

## Resumo

A osteogénese imperfeita, conhecida como doença dos ossos frágeis, é uma condição genética que afeta a matriz extracelular do sistema esquelético, causando fragilidade óssea e possíveis impactos em outros órgãos. Sua prevalência varia de aproximadamente 1 em 10 000 a 20 000 nascimentos e está associada a várias mutações genéticas. Relato de caso de paciente feminina de 14 meses com diagnóstico de osteogênese imperfeita tipo III, caracterizada por baixa estatura, problemas na formação de dentes e fragilidade óssea. Histórico médico inclui febres, questões gastrointestinais e respiratórias tratadas eficazmente. Radiografias mostraram fraturas nos fémures e úmeros bilaterais. Submetida a cirurgia no fémur e continua com fraturas frequentes, sem capacidade de locomoção, sob cuidados médicos intensivos. A osteogênese imperfeita é uma condição genética com fragilidade óssea severa, baixa estatura e deformidades progressivas, requerendo diagnóstico preciso e tratamento eficaz para melhorar a qualidade de vida.

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**Recebido/Received:** 15/07/2024 **– Aceite/Accepted:** 01/02/2025 **– Publicado online/Published online:** 13/02/2025 **– Publicado / Published:** 31/03/2025

**Keywords:** Child; Osteogenesis Imperfecta

**Palavras-chave:** Criança; Osteogénese Imperfeita

## Introduction

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a genetic defect affecting the extracellular bone matrix. Its primary characteristic is bone fragility, but it can also affect other organs. Additionally, dental issues known as dentinogenesis imperfecta, and soft tissue abnormalities such as blue sclera and joint hypermobility are commonly observed.[1]

The main cause of OI lies in mutations of two genes responsible for encoding type I collagen. This protein is a heterotrimer composed of two α1(I) chains and one α2(I) chain. Initially synthesized as a procollagen molecule, it undergoes several post-translational modifications. The removal of the flanking propeptides occurs via specific proteases, resulting in the spontaneous assembly of the molecule.[1]

OI affects approximately 1 in 10 000 to 20 000 births. It is a genetically heterogeneous disease characterized by skeletal dysplasia caused by different genetic mutations. Unfortunately, this condition presents a higher mortality rate than that found in the general population.[1] We report here a case of OI and review the literature on this rare genetic alteration.

## Case Report

Female 14-month-old patient, delivered via cesarean section at full term. The child was diagnosed with Type III OI, according to Sillence classification, due to multiple fractures. The diagnosis was made after the identification of an intrauterine fracture through ultrasound during the gestational period. The patient presents currently with short stature, dentinogenesis imperfecta, and extreme bone fragility.

She has a history of fever and gastrointestinal complications such as diarrhea and gastroenteritis requiring antibiotic therapy, as well as respiratory complications including severe bronchospasm necessitating antibiotic therapy (ceftriaxone), salbutamol, and beclometasone, which led to improvement in respiratory effort. Two years ago,-radiographs showed diaphyseal fractures of both the femurs and the right humerus. She underwent non-operative reduction surgery for the femoral fracture. The patient continues to experience frequent fractures with no prognosis for ambulation. She is under regular orthopedic outpatient follow-up to monitor residual deformities.

## Discussion

To classify the severity of OI bone fragility based on clinical and radiological characteristics, Sillence *et al* proposed a classification in 1979 that divided OI into four phenotypic categories:

- Type I - non-deforming OI with blue sclera.
- Type II - perinatally lethal OI.
- Type III - progressively deforming OI.
- Type IV - moderate to severe OI.[2]

In 2004, Glorieux and Rauch expanded Sillence's classification by adding types V-VII of OI, involving unknown genetic defects with presumed autosomal dominant inheritance (OI type V) and autosomal recessive inheritance (OI types VI and VII).[1,2]

The pathophysiology of OI involves reduced production of type I collagen, approximately half of the normal amount, due to the effect of a null allele. Additionally, there is secretion of mutated procollagen type I molecules incorporating mutated pro-α1(I) or pro-α2(I) chains, in a dominant-negative mechanism. Studies in human osteoblasts in OI indicate not only decreased collagen levels but also a reduction in other bone matrix glycoproteins such as osteonectin, chondroitin sulfate proteoglycan, biglycan (PGI), and decorin (PGII). Tissue culture studies show an altered presence of these proteins, with lower concentrations of osteonectin and proteoglycans and higher concentrations of thrombospondin, fibronectin, and hyaluronic acid in the matrix. Despite mutations predominantly occurring in *COL1A1* and *COL1A2* genes related to procollagen type I, the interaction between these mutations and the synthesis of other extracellular matrix proteins suggests a connection between type I collagen defects, compromised cell growth, and clinical manifestations of OI, such as characteristic reduced stature.[3]

The fundamental clinical feature is bone fragility, present in all types of OI, although other extra-skeletal characteristics may occur. The key aspects of each type, according to the clinical classification by Van Dijk and Sillence, are as follows:

- Type I: Associated with low bone density, rare fractures at birth but increasing in long bones over time. Blue or gray sclera and increased risk of early hearing loss are common, while long bone or spine deformities and dentinogenesis imperfecta are less frequent.
- Type II: Severely affected bones with short and severely deformed long bones. Poor ossification of facial and cranial

bones is detected on fetal ultrasound, and multiple rib fractures are observed in utero, resulting in high perinatal lethality.

- Type III: Characterized by severe bone fragility and progressive skeletal deformity, with generalized osteopenia and fractures present at birth. Blue sclera and dentinogenesis imperfecta may be present, but the bluish hue tends to diminish over time. Short stature is common, and progressive kyphoscoliosis begins in childhood.
- Type IV: Patients experience recurrent fractures with variable deformity. Most have normal sclera, and hearing loss is rare. Severity varies within families, presenting with milder forms in some individuals and more severe forms in others.
- Type V: Characterized by progressive calcification of the interosseous membrane and hyperplastic callus, with moderate to severe bone fragility but no presence of blue sclera or dentinogenesis imperfecta.[1]

Dental abnormalities are common. The dental expression of OI is known as dentinogenesis imperfecta, a genetic condition affecting dentin structure and tooth appearance, characterized by distinctive brown-gray discoloration.[2,4]

A study conducted by Martin *et al*[3] highlights that the incidence of functional constipation in children with OI is significantly higher compared to the general pediatric population, which shows considerable variation. Although rates of urinary and fecal incontinence are lower in children with OI compared to those with neurological and intellectual disabilities, functional constipation remains a more prominent concern in this group. Bladder symptoms in children with OI have been reported on a smaller scale compared to previous studies on functional constipation. Underlying causes of constipation in children with OI include mobility difficulties, bone deformities, and side effects of bisphosphonate treatment. Fractures in children with OI can lead to bone remodeling and pelvic narrowing, especially in cases of OI type III, where two-thirds of adults present with acetabular protrusion associated with chronic constipation and abdominal pain.[4]

In OI, changes such as hyperkyphosis, scoliosis, rib fractures, and pectus carinatum affect the structure of the chest wall, potentially restricting diaphragmatic movement due to upward compression of abdominal contents resulting from short stature. These physical modifications can contribute to inadequate airway clearance, increasing the risk of infections.[5]

Differential diagnosis from other conditions such as idiopathic or juvenile osteoporosis, campomelic dysplasia (CD), and severe hypophosphatemia is necessary. Additionally, considering the possibility of child abuse as a cause of multiple fractures, especially in the first year of life, is important.[1,6]

Some instances of uncertain diagnosis may indeed result from mutations in *COL1A1* or *COL1A2* genes, common in OI. Although diagnosis primarily relies on clinical and radiological findings, genetic testing plays a crucial role in accurately determining the cause of the disease, especially in less evident cases. Molecular analysis enables identification of the specific type of OI (dominant or recessive) and the identification of affected family members. This is particularly valuable in situations of mild forms of type I OI, where clinical signs may be subtle. However, it is important to note that molecular diagnosis has limited impact on the evaluation of suspected child abuse and in infants whose clinical examination does not reveal typical features of OI.[1]

The therapeutic approach for patients with OI depends on age, disease severity, and functional status of the patient. Patients with mild forms of the disease may require subtle restrictions, such as avoiding contact sports. Intravenous bisphosphonate treatment has shown positive results, while oral bisphosphonates have not demonstrated the same impact. Tiley and Albright recommended delaying the use of intramedullary rods until the child begins weight-bearing. Intramedullary rod application was initiated in children at least 4 years old. However, surgical intervention may be considered in cases where optimizing functionality and mobility capacity is necessary. Ryöppy et al highlighted that early stabilization of affected bones may be necessary to prevent disruption in motor development caused by a cycle of fractures, immobilization, osteoporosis, refractures, and reduced motor activity due to fear of new fractures. Several researchers have reported positive outcomes by recommending surgical interventions in childhood, using "percutaneous" and "semi-closed" approaches for non-lengthened rods in the treatment of severely affected patients.[1,2,7]

In conclusion, we report a case of OI type III. OI is a genetic condition characterized primarily by bone fragility. From Sillence's initial classification in 1979, which outlined four main types, to subsequent expansions that introduced new variants, OI is marked by distinctive skeletal deformities and, in some cases, extra skeletal manifestations such as functional constipation and dental anomalies. Diagnosis relies on clinical findings, imaging studies, and increasingly, genetic testing to identify specific mutations. Management is multifaceted, involving supportive care, bisphosphonate therapy, and targeted surgical interventions aimed at enhancing mobility and improving quality of life for patients.

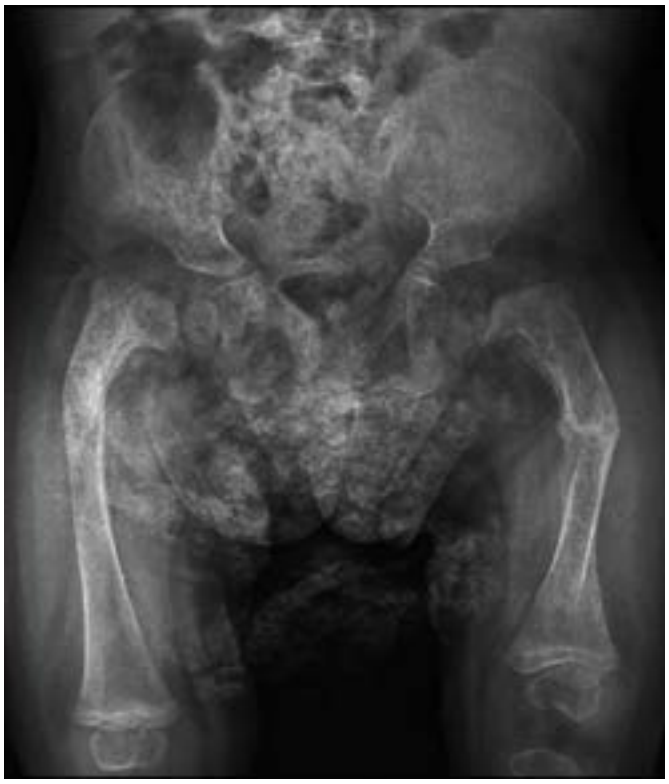

**Figure 1.** Lower limb X-ray, anteroposterior view, showing a healed and remodeling diaphyseal fracture of the right femur and a diaphyseal fracture of the left femur in the process of healing.

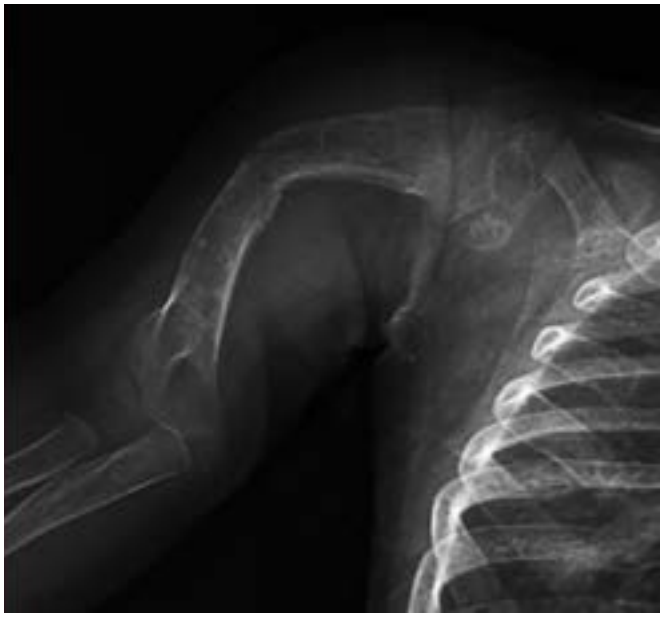

**Figure 2.** Right humerus X-ray, anteroposterior view, demonstrating a diaphyseal fracture of the humerus consolidated in a malaligned position.

## Ethical Disclosures

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Financing Support:** This work has not received any contribution, grant or scholarship.

**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of data from patients.

**Patient Consent:** Consent for publication was obtained

**Provenance and Peer Review:** Not commissioned, externally peer reviewed.

## Responsabilidades Éticas

**Conflitos de Interesse:** Os autores declaram não possuir conflitos de interesse na realização do presente trabalho.

**Suporte Financeiro:** Não existiram fontes externas de financiamento para a realização deste artigo.

**Confidencialidade de Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

**Consentimento:** Consentimento do doente para publicação obtido.

**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

## Contributorship Statement

**NG, RF MR, SH and AR:** Data curation, formal analysis, research, methodology, validation, visualization, original draft writing, writing - proofreading and editing.

All authors approved the final version.

## Declaração de Contribuição

**NG, RF MR, SH e AR:** Curadoria de dados. análise formal, pesquisa, metodologia, validação, visualização, escrita do manuscrito, revisão e edição.

Todos os autores aprovaram a versão final.

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