

Case Report

Diagnosis and Management of Type 4-IV Osteogenesis Imperfecta from Intrauterine Life to School Age: A Clinical Case Study

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Abstract

Osteogenesis imperfecta (OI) is a genetically heterogeneous hereditary disorder characterized by increased bone fragility, leading to recurrent fractures following minimal or no trauma. In 2009, the International Nomenclature Committee for Constitutional Disorders of the Skeleton (INCDS), and as published in the 2010 Nosology, OI was reclassified into five major types. Type IV OI is caused by mutations in the COL1A1 and COL1A2 genes, which are responsible for the synthesis of type I collagen, a critical component of bone matrix. These mutations result in varying degrees of bone deformity, growth retardation, and other systemic manifestations. In this report, we present a case of antenatal diagnosis of OI, providing a comprehensive overview of the disease's evolution from the intrauterine stage through early childhood and into school age. This case illustrates the wide phenotypic variability of OI, with clinical manifestations spanning the prenatal period, birth, infancy, and school years, and highlights the multiple complications encountered at each stage of development. The profound impact of the disorder on the patient's daily functioning and the family's quality of life is also discussed.

Keywords

Children, Osteogenesis Imperfecta, Growth Retardation, Pathological Fractures, Antenatal Diagnosis

1. Introduction

Osteogenesis imperfecta (OI), also known as "brittle bone disease," is a rare genetic disorder characterized by increased bone fragility [1]. Its incidence is estimated to be between 1 in 10,000 and 1 in 20,000 live births [2]. This condition is caused by mutations in COL1A1 and COL1A2 genes encoding for collagen proteins, essential for bone tissue formation and stability [3]. The diversity of genetic mutations involved in OI results in a wide clinical variability, ranging from mild to severe forms with significant complications [4].

OI type IV is a moderately deforming form of the disease, often associated with short stature and variable bone fragility [5]. In this article, we aimed to explore the clinical evolution of a specific case of OI type IV, from fetal life to school age, while conducting a literature review on this condition. The objective was to review the clinical features of OI type IV and the challenge faced in its management, to gain a better understanding of the disease manifestations at different stages of life.

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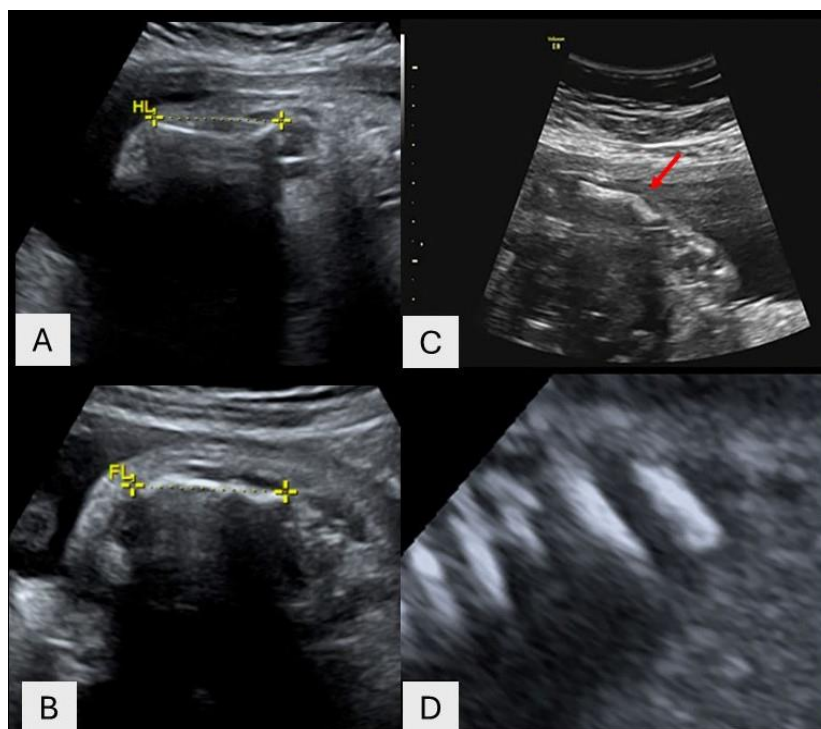


Figure 1. Fetal ultrasound examination revealed shortened and deformed long bones.

A: Humerus
B: Femur B
C: Right fibula with altered morphology.
Red arrow indicates a point fracture. D. Multiple ribs fractures.

2. Observation

The observation involves a boy born to non-consanguineous parents, with the mother aged 31 years.

2.1. Fetal Life

The mother was gravida 1 para 0, with a history of primary infertility due to polycystic ovarian syndrome. She got pregnant after ovarian stimulation cycle by clomiphene citrates. The pregnancy was regularly monitored by a general practitioner. The patient skipped the second trimester ultrasound screening and showed at our department at 29 weeks of gestation. Ultrasound examination revealed intrauterine growth restriction (estimated fetal weight lower than the 3rd percentile) with shortened and deformed long bones (Figure 1A, 1B), a suspected right fibula fracture (Figure 1C) and multiple ribs fracture (Figure 1D). Fetal skeletal computed tomography (CT) was ordered to better explore this micromelic dwarfism. It showed curved lower limbs with a fracture to the right fibula and to the ribs without bone callus, suggesting OI (Figure 2). The baby was delivered via planned cesarean section at 38 weeks of gestation to avoid the risk of fracture and adapted well to extra-uterine life.

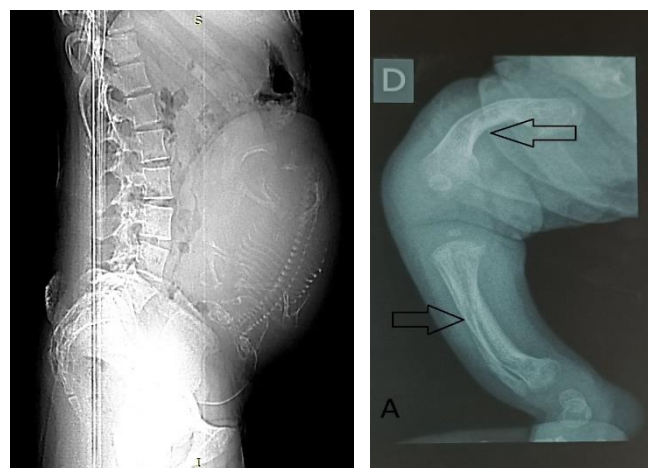


Figure 2. Fetal life: Fetal skeletal CT (SCOUT) showing short, curved lower limbs with fractures to the right fibula and ribs without bony callus.

2.2. Neonatal Period

At birth, the baby presented severe symmetrical growth retardation, with weight, height, and head circumference below the 3rd percentile. The baby had short and curved upper

and lower limbs, along with a healing posterior rib fracture (Figure 3). There was no vertebral compression, and no respiratory distress was observed at birth. Family history revealed similar cases of the disease in a maternal cousin and aunt. Based on the clinical and radiological characteristics, the diagnosis of OI type IV was highly suspected.

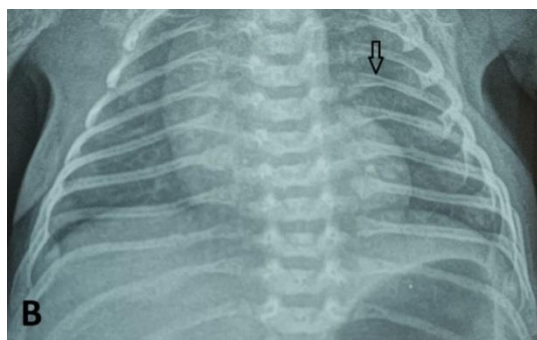


Figure 3. Neonatal period.

- A. Short and curved femurs, tibiae, and fibulae with an image of a healing fracture in the lower third of the diaphysis of the right fibula and tibia.
- B. Consolidation in progress of a fracture of the posterior arch of the 10th rib.

2.3. Treatment and Evolution up to School Age

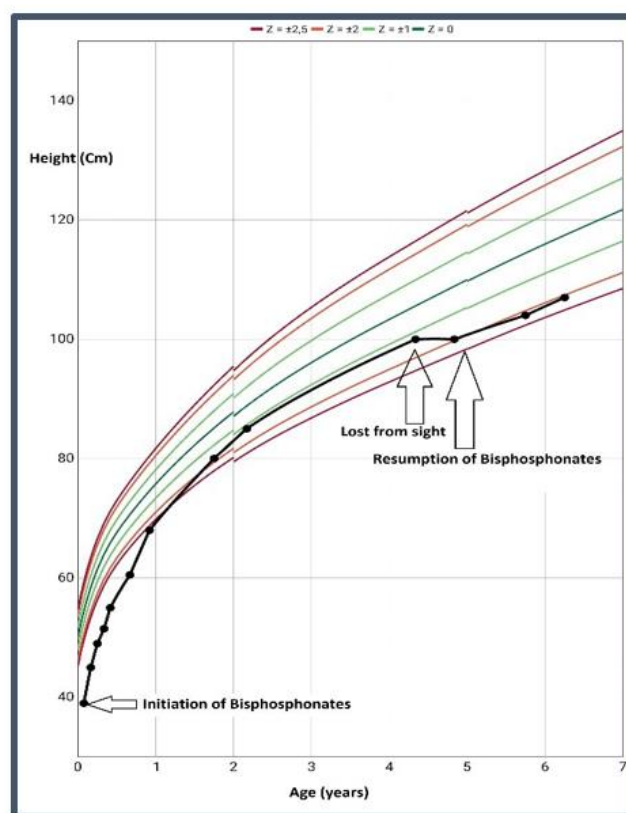
Bisphosphonate treatment was initiated at one month of age, starting with intravenous Pamidronate 0.5 mg/kg every two months, with increasing doses as the patient aged while spacing the cycles. At the age of seven years, the patient receives intravenous Pamidronate 1 mg/kg/day for three days every four months, combined with oral calcium supplementation.

The patient's growth showed marked improvement under treatment (Figure 4). Although the cranial circumference remained below the 10th percentile until the age of six months, it caught up afterward. The improvement in stature growth (between -1 and -2 standard deviation (SD)) observed from one year of age was not correlated with the improvement in weight growth (+2 SD). Consequently, the patient's body mass index gradually increased and currently exceeds the 97th percentile, which further increases the risk of fractures. During the COVID-19 pandemic, parents' fear of contracting COVID-19 was the main reason for missing Bisphosphonate doses. Temporary treatment interruption resulted in a growth curve break and femur fracture requiring intramedullary nailing. Under bisphosphonate treatment, the number of fractures has significantly decreased. The patient has been fracture-free for over two years. Due to the femur fracture requiring intramedullary nailing, the patient now has a residual limp and occasional pain at previous fracture sites. The sclera remained white, and imperfect dentinogenesis started at

the age of seven months, characterized by the translucency of primary and permanent teeth (Figure 4). According to Aglan scoring, the disease was mild. Audiometry at the age of five showed no abnormalities, and there were no respiratory issues. A bone density test was not performed due to availability and financial constraints. The disease significantly impacted the child's and parents' quality of life. Frequent hospitalizations have delayed the patient's schooling, and the mother had to quit her job to care for her child and accompany him to various appointments and multiple hospitalizations.

3. Discussion

OI type IV typically presents with severe bone fragility, resulting in multiple fractures, short stature, and skeletal deformities [6]. The case presented involves a boy infant born to non-consanguineous parents, exhibiting severe symmetrical growth retardation, short and curved limbs, and a healing rib fracture at birth. Notably, family history revealed similar cases within close relatives, suggesting a genetic basis consistent with autosomal dominant inheritance [7]. Van Dijk and Sillence [8] offered a comprehensive review of the clinical diagnostic criteria for OI, emphasizing the importance of accurate phenotypic characterization and classification in guiding management and prognosis.



A



B1



B2

Figure 4. Childhood.

- A. Height (cm) relative to age (years) according to the WHO curve.
 B. B1- Imperfect dentinogenesis, characterized by amber-colored teeth, B2- A white sclera suggesting Osteogenesis Imperfecta type 4.

Diagnostic confirmation often involves a combination of clinical evaluation and radiological findings [6]. In this case, fetal skeletal CT played a crucial role in identifying micromelic dwarfism with characteristic fractures, guiding timely intervention and delivery planning. Rauch and Glorieux [9] discussed the clinical presentation of OI in detail, highlighting the variability in severity, ranging from mild to severe forms, and the significance of distinguishing between different types based on clinical and radiographic features. Postnatally, clinical and radiological features corroborated the diagnosis of OI type IV, highlighting the importance of comprehensive assessment in confirming the diagnosis. Biggin and Munns [10], provided insights into the clinical evaluation and diagnostic workup of OI, emphasizing the role of radiological imaging, genetic testing, and multidisciplinary assessment in establishing a precise diagnosis and guiding management decisions.

OI is caused by mutations in genes encoding collagen proteins, essential for bone tissue formation and stability [11]. The diverse genetic mutations involved in OI, result in a wide clinical variability, ranging from mild to severe forms associated with major complications [8]. The diagnosis of OI is primarily clinical and can present with various phenotypes [5]. The Silence classification, based on clinical and radiological characteristics, is currently used to assess disease severity [6].

Additionally, a functional classification based on the metabolic pathway helps identify regulatory factors and target specific therapeutic approaches [12]. In our observation, the diagnosis of OI was suspected based on family history and the results of prenatal ultrasound and CT, showing micromelic dwarfism and a fibula fracture [13]. The combination of ultrasound, CT, and MRI can not only accurately detect OI but also predict lethality before birth [3, 14]. Genetic testing is essential for identifying pathogenic variants, mode of transmission, and differential diagnosis [12]. Sequencing of COL1A1 and COL1A2 genes or comprehensive next generation sequencing panels is recommended based on clinical, radiographic features, and family history [12, 15].

To minimize the risk of fractures during uterine contractions, the mother opted for a scheduled cesarean section delivery. Cesarean delivery was considered safer and more useful for preventing fractures at birth than vaginal delivery. Bellur et al. [16] on babies with OI types I, III, and IV have shown that the mode of delivery does not influence the rate of fractures at birth. Additionally, breech presentation appears to be more common in OI type III [16, 17] Bellur et al. [16] suggested that cesarean delivery should only be performed for usual maternal or fetal indications, not for preventing fractures in OI.

Regardless of the delivery method, the pediatrician must attend the birth of a newborn suspected of having OI. This newborn may present not only severe intrauterine growth retardation (IUGR) [18], but also severe bone fractures, a small chest, and short and wide ribs, potentially leading to respiratory distress, especially in OI type 2 [19]. As described in our observation, the main complication of the disease is the occurrence of multiple fractures [5]. Surgical procedures are used for complex fractures or when correction of deformities is necessary. Intramedullary telescopic rods are used during growth due to their ability to elongate [14, 17]. Surgeons must consider the anesthetic risks in OI patients due to abnormal airways, impaired lung function, or the possibility of cervical spine fracture during intubation [20].

The main goals of managing OI are fracture and deformity prevention, maximizing the patient's functional capacity, and reducing pain [17, 21]. Bisphosphonates are commonly used to increase bone density and reduce the risk of fractures [22]. If Bisphosphonate treatment fails, alternative treatments such as Denosumab may be used [22]. Denosumab is considered a strong candidate for OI patients with bone fragility and a high risk of fractures, particularly for patients with OI-VI subtype insensitive to bisphosphonates [22]. A multidisciplinary approach is recommended to address issues related to bone fragility and extra-skeletal manifestations [23].

OI also affects growth, mainly height [23]. Extreme short stature is a cardinal feature of severe OI, types III and IV [23]. This leads to a high body mass index, further increasing the risk of fractures [24]. Growth hormone (GH) treatment for these patients is debatable [23]. As bisphosphonates inhibit bone resorption by osteoclasts and GH affects bone formation,

both drugs have the potential to be synergistic [23]. Some authors have shown that exogenous GH treatment can compensate for the matrix defect in OI and substantially increase linear growth rates in many children with OI type IV [18, 21]. Our patient could not receive GH treatment due to lack of social coverage.

Other manifestations of the disease are possible, such as a grayish sclera, frequent hearing loss, emphasizing the importance of audiometry monitoring, ligamentous laxity, skin fragility, delicate capillaries resulting in bruising and nosebleeds, imperfect dentinogenesis, characterized by amber-colored teeth and a more globular shape, and dilations, aneurysms, or ruptures of cardiac chambers, aorta, or cerebral blood vessels [24, 25]. It should be noted that the severity of the disease can vary considerably from one patient to another.

The impact of OI on the patient's daily life is significant, as evidenced by the mother's decision to leave her job to provide care and accompany the child to various appointments and hospitalizations. This highlights the emotional, financial, and social burden experienced by parents of children with OI [26, 27]. It is important for patients and their families to receive comprehensive support, including regular medical follow-up, psychological support, occupational and physiotherapy services, as well as access to support groups and community resources. A multidisciplinary approach allows for addressing the complex needs of the disease and improving the quality of life for the patient and their family [25, 27].

Regardless of the delivery method, the pediatrician must attend the birth of a newborn suspected of having OI [28]. This newborn may present not only severe IUGR [18], but also severe bone fractures, a small chest, and short and wide ribs, potentially leading to respiratory distress, especially in OI type II [19]. As described in our observation, the main complication of the disease is the occurrence of multiple fractures [5]. Surgical procedures are used for complex fractures or when correction of deformities is necessary [17]. Intramedullary telescopic rods are used during growth due to their ability to elongate [14, 17]. Surgeons must consider the anesthetic risks in OI patients due to abnormal airways, impaired lung function, or the possibility of cervical spine fracture during intubation [20].

Conclusion:

Through this clinical case illustrating the evolution of OI type IV, we have highlighted the crucial importance of clinical and radiological signs in the early diagnosis of this hereditary disease. A multidisciplinary approach is essential for comprehensive and tailored management of patients with OI. Further research is needed to improve treatment strategies and enhance the quality of life for these vulnerable patients.

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Statement on Consent for publication: The authors certify that they have obtained the parent's consent for image and clinical information to be reported in the journal. Parent un-

derstand that the name of his baby will not be published.

Statement on Ethical approval and informed consent:

The authors consciously assure that for the manuscript, the following is fulfilled:

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- 3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
- 4) The paper properly credits the meaningful contributions of co-authors.
- 5) The results are appropriately placed in the context of prior and existing research.

Abbreviations

OI	Osteogenesis imperfecta
CT	Computed Tomography
SD	Standard Deviation

Conflicts of Interest

The authors declare no conflicts of interest.

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