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Challenges in managing osteogenesis imperfecta in a resource-limited setting: a case report

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Abstract

Introduction Osteogenesis imperfecta is a rare inherited connective tissue disorder that results in excessive bone fragility due to defects in collagen production. The majority of osteogenesis imperfecta cases are inherited in an autosomal dominant pattern, and 17 genetic causes have been identified. Diagnosis is usually based on clinical presentation and low bone mineral density scores, while treatment involves a multidisciplinary approach using medical therapies such as bisphosphonates, vitamin C, and pamidronate. Recent research has also explored new therapies, including teriparatide, denosumab, and allele-specific silencing (Edelu *et al*. in *Ann Med Health Sci Res* 4(Suppl 1):S1–5, 2014; Bastos *et al*. in *Einstein* (São Paulo) 8:480–2, 2010; Van Dijk and Sillence in *Am J Med Genet A* 164A(6):1470–81, 2014; Subramanian and Viswanathan in *Osteogenesis Imperfecta*. In: StatPearls. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK536957/. Accessed 2 Mar 2023, 2022).

Case presentation A 3-week-old female neonate of African ethnicity was delivered at term by emergency C-section due to two previous scars. The baby had an APGAR score of 7 at 5 minutes and a birth weight of 2.5 kg. The neonate had short and deformed limbs, a soft head, and bluish eyes. The neonate was diagnosed with osteogenesis imperfecta on the basis of clinical examination findings and radiological investigations, which showed multiple bony discontinuities at variable stages of healing in the limbs and ribs. The neonate was managed with supplemental oxygen by nasal prongs and intravenous antibiotics but unfortunately passed away before being reviewed by the orthopedic team.

Conclusion This case report underscores the importance of early diagnosis of osteogenesis imperfecta and highlights the need for increased clinical awareness, specialized training, and resource allocation to improve outcomes for patients with rare genetic disorders in low-resource settings.

Keywords Osteogenesis imperfecta, Neonate, Resource-limited setting, Fragile bones, Connective tissue disorder

Introduction

Osteogenesis imperfecta (OI) is a group of rare inherited disorders of connective tissue with the common feature of excessive fragility of bones as a result of quantitative and qualitative abnormalities in type 1 collagen in more than 90% of the patients [1]. Most of the cases (types I–V) are inherited in an autosomal dominant pattern of transmission, with just a few variants transmitted autosomal recessively and de novo

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mutation [2]. At present, a total of 17 genetic causes of OI have been described [3]. An internal deletion in the collagen gene (*COLIA1*) has been noted. Mutations in *COLIA1* and *COLIA2* genes encoding, respectively, the alpha 1 and alpha 2 chains of collagen type 1 were detected in all types of OI [3]. These mutations reduce the amount of collagen type 1 produced, leading to bone fragility and multiple fractures [2]. Apart from collagen type 1 mutation, other genetic mutations producing autosomal recessive types of OI (types VI, VII, VIII, X, and XI) have been described, but these account for less than 5% of OI. OI type II is the perinatal lethal form [4].

It is the most common connective tissue disorder, though rare, with an estimated incidence of 1 per 20,000 live births [5]. The incidence of type II OI ranges between 1 in 40,000 and 1.4 in 100,000 live births [4]. In the *East African Orthopedic Journal*, the prevalence of OI in Kenya was reported to be 80 patients with 57.5% male and 42.5% female, with the eldest being 30 years and the youngest 3 years [6]. The clinical presentation is dependent on the type of OI. The presentation is characterized by multiple and recurrent fractures, which are intrauterine, perinatal, or postnatal. Other features include blue sclera, otosclerosis with hearing loss, high arched palate, hyperlaxity of ligaments and joints, "dentinogenesis imperfecta," and growth retardation [1]. Postnatally, the thighs are held in a fixed abduction and external rotation with limitation of movements of most joints. It can present with respiratory distress leading to perinatal death [3].

Investigative confirmatory genetic tests are not available in East Africa, especially in Uganda. Laboratory values are typically within the normal range [4]. A plain radiograph of the head, neck, and spine may show Wormian bones, basilar invagination, and kyphoscoliosis (39–100%), while the chest may show pectus excavatum or carinatum. Biopsy of the iliac crest bone demonstrates a decrease in cortical widths and volume of cancellous bone and collagen analysis of a punch biopsy.

In practice, the diagnosis of OI is by exclusion, fortified by consistent clinical presentation, family history, and low bone mineral density scores. Specialized investigations are rarely warranted [7]. The management of OI is multidisciplinary, involving medical therapies, including sex hormones, sodium fluoride, calcium, calcitonin, magnesium oxide, vitamin C, and bisphosphates (intravenous pamidronate, oral alendronate) [1, 4]. Pamidronate does not alter the genetic defect underlying OI and therefore is asymptomatic and not curative [8]. Among the new therapies are teriparatide, denosumab, and transforming growth factor-beta [9]. Another approach is allele-specific silencing, which models the null *COLIA*.

Case presentation

A female neonate of African ethnicity who was 3 weeks old was referred to St. Mary's Hospital Lacor from Dr. Ambrosolio Memorial Hospital Kalongo. The baby was delivered via emergency C-section to a 23-year-old para 3 mother who had 2 previous scars. The APGAR score at 5 minutes was 7, and the birth weight was 2.5 kg. The baby was admitted to the newborn unit at Kalongo hospital due to breathing difficulties and poor feeding. The neonate had short and deformed limbs, a soft head, and bluish eyes from birth. The mother attended ANC seven times, starting at 16 weeks of amenorrhea (WOA) and taking folic acid at 16 WOA. There was no family history of congenital birth defects, and the mother had no history of maternal drug or medicine use during pregnancy. However, she had a febrile illness during pregnancy that was treated as malaria.

On physical examination, the baby was stable but mildly hypothermic with an axillary temperature of 36.0 ℃ and easily agitated. There was no pallor or jaundice, but the sclera was bluish, and there was mild exophthalmos. The head circumference was 34 cm, with a wide and full anterior fontanelle continuous throughout the sagittal suture. The occiput was soft with no palpable occipital bone. The musculoskeletal system showed that all four limbs were malformed and shortened with multiple pseudo joints (Fig. 1). The respiratory system

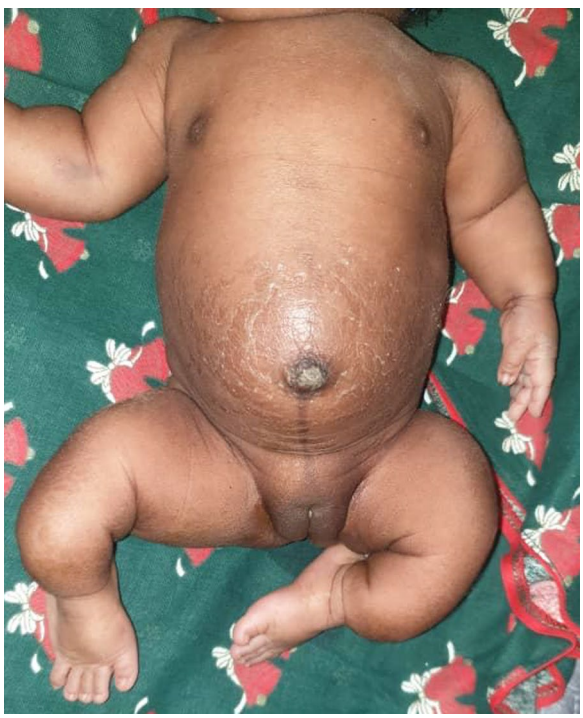

Fig. 1 Showing multiple pseudo joints of the neonate

had dyspnea with a respiratory rate of 64 cycles per minute. The cardiovascular system showed warm peripheries with full-volume pulses, a heart rate of 160 beats per minute, and normal heart sounds. The abdomen had mild distention with an occult anterior wall defect, no palpable enlarged organs, and normal bowel sounds.

Radiological investigations showed multiple bony discontinuities (fractures) at variable stages of healing in the limbs and ribs. The limbs also had what appeared to be pseudo joints. Cranial ultrasound and echocardiography were normal. Laboratory investigations revealed a white cell count of 8500 cells/μL, hemoglobin of 11.0 g/dL, platelet count of 414,000 cells/μL, and slightly high potassium of 5.3 mmol/L.

The baby was diagnosed with osteogenesis imperfecta on the basis of clinical and radiological findings. The baby was admitted to the neonatal intensive care unit and put on supplemental oxygen by nasal prongs, intravenous ampicillin 100 mg 12 hourly for 5 days, and intravenous gentamicin 6.0 mg once a day for 5 days. The baby was fed through a nasogastric tube, but unfortunately, her respiratory distress worsened over time, and she passed away before the orthopedic team could review her. No genetic analysis was conducted or medical therapies started.

Discussion

OI is a condition that is rarely reported in Africa and among Black populations in other regions. Its primary characteristic is the fragility or brittleness of bones, which can lead to multiple fractures even after minor trauma. The diagnosis of OI is typically based on clinical and radiological examinations, and in some cases, collagen or genetic analysis may be necessary. In the case of our patient, the diagnosis was made on the basis of the medical history, clinical examination, and plain x-rays of the body. While routine laboratory investigations can help rule out other metabolic bone pathologies, they were within normal ranges for our patient [5]. Our patient's complete blood count and serum electrolytes were within normal ranges. Osteogenesis imperfecta (OI) has various types, with type I being a mild form characterized by repeated fractures and blue sclera, which has A and B subtypes on the basis of the absence or presence of dentinogenesis imperfecta. Fractures are less common in this type. Type II, on the contrary, is an autosomal recessive form that is generally lethal in the perinatal period, with multiple congenital fractures, micromelia, and severe lung disease. Our patient exhibited multiple fractures, blue sclera, and severe lung disease evidenced by marked respiratory distress and hypoxia (SPO_2 of 89–90%) with short, malformed limbs. Unfortunately, she died at 3 weeks old due to marked respiratory distress. The presence of Wormian bones could not be demonstrated as a skull x-ray was not performed. The cause of respiratory distress is pulmonary hypoplasia due to the direct role of mutant collagen in lung pathology, as reported by Forlino *et al.* [10]. Restrictive lung disease due to spinal deformity and rib fractures could also have contributed to the lung disease, as noted by Strevel *et al.* [7]. The patient did not exhibit any spinal deformity or rib fractures and had a normal echocardiography ruling out valvular insufficiency, aortic root dilation, atrial septal defects, and septal and posterior left ventricular wall thickening, which are typically observed in osteogenesis imperfecta (OI) type II [2, 7, 10]. Although there was no family history of OI, sporadic mutations are common in type II OI, and prenatal diagnosis through ultrasonography is possible [1]. However, due to the inaccessibility of the service, prenatal ultrasonography was not performed in this case.

OI type II is associated with a poor prognosis and raises ethical concerns regarding termination of pregnancy upon detection. Poor prognosis indicators include the age of onset of long bone fractures, fracture location, fracture severity, and radiographic appearance of the skeleton [4]. Our patient had a poor prognosis due to multiple long bone fractures.

OI types III and IV are intermediate phenotypes, with type III being a severe nonlethal form that results in marked bony deformity due to multiple fractures, which can be congenital [1, 4]. The management of OI requires a multidisciplinary approach, including pediatricians, orthopedic surgeons, anesthetists, geneticists, and physiotherapists. Unfortunately, our patient passed away before any other specialists could be involved, including orthopedic surgeons and other relevant disciplines.

Bisphosphonates are effective in the symptomatic treatment of OI in children and adolescents [11]

According to a study, cyclic pamidronate infusions were found to significantly improve bone density and decrease fracture rates in severely affected patients with OI under 3 years of age without any major adverse side effects [8]. In a separate randomized controlled study, quarterly intravenous neridronate infusions were found to significantly increase bone mineral density and lower the risk of clinical fracture in prepubertal children with OI [12]. Another treatment option is denosumab, a monoclonal antibody that targets RANKL to prevent osteoclast formation and decrease bone resorption. The first 2-year data of denosumab in patients with OI type IV and in OI, in general, was reported as an effective and safe treatment option in the *Orphanet Journal of Rare Disease* [13].

According to Edelu *et al.*, various drugs have been used to treat OI, including sex hormones, sodium

fluoride, calcium, calcitonin, magnesium oxide, and vitamins A, C, and D. Growth hormone therapy has also been tried in children with type I OI and type III/IV, resulting in significant improvements in linear growth and bone histology [10]. However, these drugs are expensive and not readily available in certain settings, such as the one in which our patient was being treated. Unfortunately, the patient passed away before she could receive an orthopedic consult, and even if she had, she may not have been stable enough for corrective surgery. Furthermore, specialized orthopedic surgeons for patients with OI are not available in our setting. Currently, there are no established physiotherapeutic treatment protocols for patients with OI [9]. Rehabilitation and physical therapy aim to enhance the patient's gross motor function and daily life skills [10]. In cases where surgical intervention is necessary, osteotomies of long bones with intramedullary rod placement may be performed to correct deformities and prevent future fractures [4].

Individualized rehabilitation programs are utilized in children with OI to promote increased strength and mobility. Validated functional tests such as Brief Assessment of Motor Function (BAMF), Gross Motor Function Measure (GMFM), and Bleck score are used to assess mobility, with muscle strength being the best predictor of mobility [9]. Various exercises, including resistance training, body-weight-supported treadmill training, neurodevelopmental treatment, and side alternating whole-body vibration, have shown improvement in mobility, lean mass, and bone mineral density in 0–6 months [9]. However, there are limited data regarding physiotherapy in infants less than 1 month old with OI type II. It is crucial to educate parents regarding survival rates, potential deformities, disabilities, and mobility capacity. The mother of the child was counseled on these matters, and genetic counseling and prenatal screening may be necessary for future pregnancies, including ultrasonography. Although the mother had two healthy children, parents with a history of a fetus affected by OI type II carry a 2–7% risk of a similarly affected fetus in future pregnancies [4]. The mother of the child was informed of the possibility of delivering a baby with OI in the future. However, due to the high cost, effective drugs such as sex hormones, sodium fluoride, calcium, calcitonin, magnesium oxide, and vitamins A, C, and D were not available in our setting, and the patient did not receive any of these treatments. Additionally, orthopedic surgery was not an option for this patient due to her unstable condition and the lack of specialized orthopedic surgeons for patients with OI in our setting.

Conclusion

Osteogenesis imperfecta (OI) is a rare inherited disorder of connective tissue that results in excessive fragility of bones. The majority of cases are inherited in an autosomal dominant pattern of transmission, with a few variants transmitted autosomal recessively and de novo mutation. Diagnosis of OI is by exclusion, and management is multidisciplinary, involving medical therapies. The case presented highlights the clinical presentation of OI and the challenges in the diagnosis and management of the disorder, particularly in resource-limited settings such as East Africa. While confirmatory genetic tests are not readily available in this region, clinical presentation and radiological investigations can help diagnose the disorder. Further research is necessary to improve the diagnosis, management, and prevention of OI.

Abbreviations

OI	Osteogenesis Imperfecta
BAMF	Brief Assessment of Motor Function
GMFM	Gross Motor Function Measure

Supplementary Information

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Supplementary Material 1.

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Author contributions

All authors contributed to the conception and design of the study, acquisition and interpretation of data, drafting and revising the manuscript, and have given final approval of the version to be published.

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Availability of data and materials

The dataset used are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

We confirm that all methods used in this study were performed in accordance with relevant guidelines and regulations, including the Declaration of Helsinki for medical research involving human participants; the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals; and any additional guidelines or regulations required by the *BMC* journal. This study was approved by the Institutional Review Board (IRB) at Lacor hospital.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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