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CASE REPORT

Osteogenesis Imperfecta in a Newborn: Case Report and Review of the Literature

Authors: Ango S, Fatunke ET, Jemide OO.

Department of Paediatrics, Federal Medical Centre, Keffi, Nasarawa State, Nigeria

*Corresponding Author Email**:** *Dr. Sarah Ango*

Department of Paediatrics, Federal Medical Centre, Keffi, Nasarawa State, Nigeria.

Email: dzeuzen2@yahoo.co.uk
Tel +234 706 154 773

Abstract

Osteogenesis imperfecta (OI) is a group of genetic skeletal disorders characterized by skeletal fragility mostly due to structural or quantitative defects in type 1 collagen. The diagnosis is often based on clinical and radiologic features, especially, in resource constrained settings.

We report the case of a term, female neonate who was delivered to a 20-year-old primipara and presented to the Neonatal Unit of Federal Medical Centre, Keffi, with respiratory distress and short deformed limbs that were noticed at birth. Radiographs revealed multiple long bone fractures and thin ribs which supported the diagnosis of osteogenesis imperfecta.

Multidisciplinary management was instituted and the infant was discharged home after 6 days on admission with resolution of the respiratory problems. She is currently being followed-up at the clinic.

Keywords: *Osteogenesis imperfecta, brittle bone disease, genetic skeletal disorder, neonate*

Introduction

Osteogenesis imperfecta (OI) also known as brittle bone disease is a group of genetic skeletal disorders with a wide spectrum of presentation.[1,2] The central feature of OI is the skeletal fragility and its predisposition to fractures as a result of structural and or quantitative abnormalities of collagen, especially, type 1 collagen found in bones, tendons, ligaments, skin, sclerae and teeth.[1]

Several genetic defects have been identified, as well as the different defective proteins. These discoveries have necessitated further genetic classification of OI in addition to an original clinical classification that describes OI syndromes.[3-6] At present, there are 5 clinical syndromes, which are mostly inherited in an autosomal dominant (AD) pattern and 20 genetic subtypes with various modes of inheritance.[5,7]

OI occurs in approximately, 1 in 20,000 live births and has no gender predilection.[1,5] The

clinical types include mild OI that is non-deforming (type 1); moderate OI (type 4); OI with calcifications of interosseous membranes and hypertrophic callus (type 5); progressively deforming OI (type 3); and perinatal lethal OI (type 2).[4,7] Osteogenesis imperfecta is a chronic, physically debilitating disorder with no cure and it impacts negatively on the quality of life and life span; this is more so in low resource settings.

Case Report

MA, a 19-day old, term, female neonate was brought to the Neonatal Unit of FMC Keffi by the mother, paternal uncle and grandmother on account of fast breathing noticed since birth and abnormal short limbs. The baby was delivered at home via spontaneous vertex delivery (SVD), supervised by the grandmother and she cried immediately after birth. The birth weight and length were not measured. Fast breathing was noticed from birth but the baby was able to suck well from the breasts without choking. There was no bluish discoloration of the lips, noisy breathing, fever, excessive crying or convulsion. The upper and lower limbs were noticed to be short and abnormally postured shortly after birth. The pregnancy was supervised at a Primary Health Care (PHC) facility and prenatal ultrasound scan was not done.

The mother had three (3) antenatal care visits and was placed on routine antenatal drugs. She also took a natural supplement (tamarind) from 7 months of gestation. The pregnancy was not adversely eventful, it was carried to term and the duration of labour and delivery were not prolonged. There was no history of trauma and no family history of short stature or similar deformities.

The parents are both from the Fulani ethnic group and first cousins. The mother is a 20-year-old primipara with no formal education or gainful employment while the father is an artisan.

Examination findings at presentation revealed a female baby with dysmorphic features, who was conscious and in respiratory distress (tachypnoeic with respiratory rate of 100 breaths/minute, flaring alae nasi and subcostal recessions). She was neither pale nor cyanosed and had an axillary temperature of 37^0C.

The dysmorphic features included, bilateral proptosis, bluish sclerae (fig. 1), low-set ears, widely-patent anterior and posterior fontanelles, flattened occiput and widely-spaced nipples. The upper and lower limbs were short, deformed and had redundant skin folds (fig. 2).

Weight at presentation was 2.6kg ($<3^{rd}$ percentile); length 41cm ($<3^{rd}$ percentile); head circumference 33cm ($<10^{th}$ percentile); chest circumference 30cm (ratio of head circumference to chest circumference 1.1:1).

Radiographs showed bowing deformity of the long bones with multiple fractures which were at various stages of healing and thinned-out ribs (fig. 3). Results of full blood count, serum electrolytes, urea and creatinine showed low haematocrit and serum calcium levels while other parameters were within the normal range.

A diagnosis of osteogenesis imperfecta was made and the baby was admitted for six (6) days within which she had correction for hypocalcaemia and received intranasal oxygen and antibiotics with resolution of the respiratory problems. The family was counseled, prior to discharge, on the child's condition and care required. The infant has been on calcium and vitamin D supplements while being followed-up on out-patient basis by the Neonatal and Orthopaedic Surgery teams.

Fig. 1: Bilateral proptosis and bluish sclerae

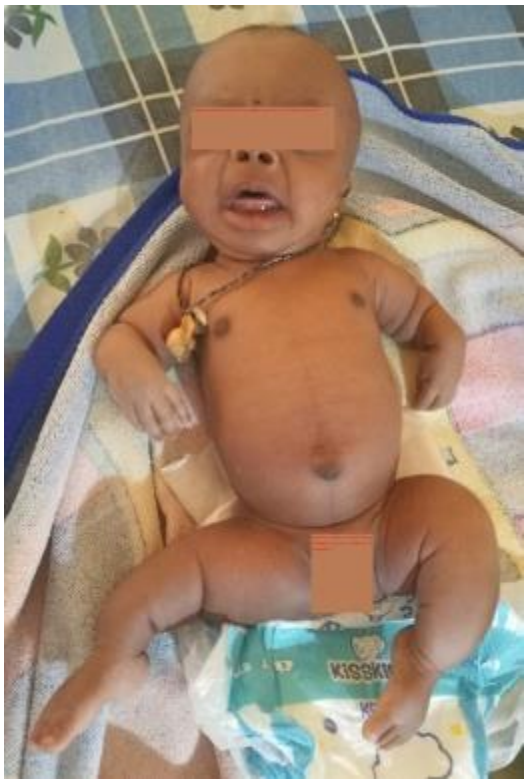

Fig. 2: Short, deformed limbs

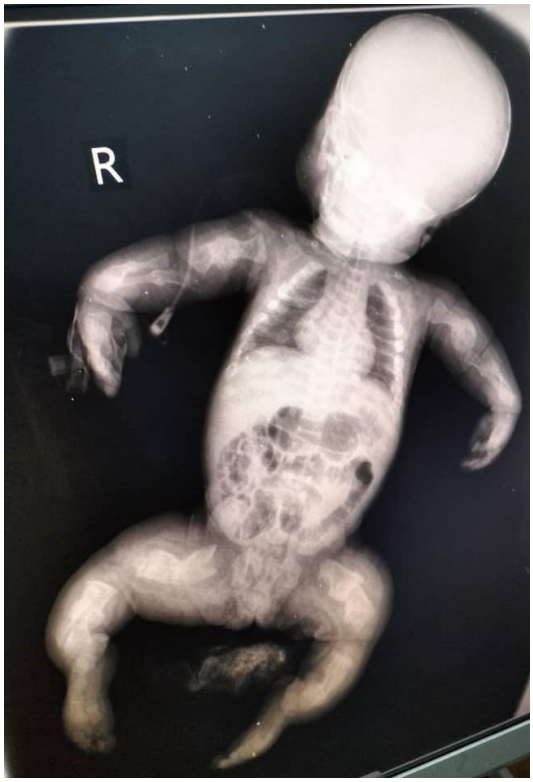

Fig. 3: Radiograph showing multiple long bone fractures at different stages of healing

Discussion

Type I collagen is the most abundant protein in the body and an important structural component of most connective tissues. It has a triple helix that consists of two alpha 1 chains and one alpha 2 chain synthesized from COL1A1 and COL1A2 genes, respectively.[5-7] Mutations in these genes result in quantitative and qualitative defects of type I collagen that account for most cases of osteogenesis imperfecta and are inherited as AD. Null mutations in COL1A1 cause haploinsufficiency of type 1 collagen and mild OI; while missense or splice mutations in COL1A1 and COL1A2 result in moderate to severe or even lethal OI.[6,7]

Mutations in genes that are involved in type 1 collagen synthesis and assembly, apart from COL1A1 and COL1A2, and genes that regulate other processes in bone formation are responsible

for 15-25% of all cases of OI and transmitted as an autosomal recessive (AR), AD or X-linked (XL) condition.[5,7] In the revised nosology and classification of genetic skeletal disorders of 2019, there is an emphasis on the genotype-phenotype correlation of OI which can facilitate counselling and treatment. Up to 20 genetic types of OI have so far been identified with some showing variable clinical severity, yet all finding expression within the 5 clinical types of OI.[2,5,7]

The clinical and radiologic features of the index case were sufficient to make a diagnosis of OI. The relatively large head, severe short stature, deformed limbs with radiologic evidence of multiple long bone fractures that occurred within the perinatal period and thin ribs in the infant suggest clinical type 3 OI.[1,7] This phenotype is progressively deforming and the most severe form of OI in those who survive the period of infancy; it constitutes 15% of all cases of OI.

Under the revised classification of OI, type 3 phenotype can be linked to 15 genotypes: type III (COL1A1 and COL1A2) inherited as AD; types VI-XI, XIII-XIV, XVI-XVIII and XX inherited as AR; and type XV (WNT1) inherited as AR/AD.[5,7] Molecular studies that could identify the abnormal genotype and be useful for genetic counselling in the index case were not readily available.

There is no ethnic predilection for AD forms of OI but AR forms can occur more frequently in some ethnic groups where consanguineous marriages are commonly practiced; the Fulani ethnic group is known for such practices and the parents of the index case are first cousins.[1,8] Molecular studies carried out on 91 people with clinical type 3 OI in a black population in South Africa identified FKBP10 (type XI) mutation in 45% of the cases and 35 of the individuals had a homozygous (AR) frameshift mutation traceable to a common ancestor.[9]

Where resources are available, identification of foetal risk factors for OI is an indication for prenatal DNA analysis of chorionic villus cells between 10-12 weeks of gestation; the option to terminate a pregnancy with perinatally lethal OI, which has a poor prognosis, is available in some of these settings.[10] Foetal ultrasonography can also be instrumental in the prenatal diagnosis of severe forms of OI and can detect in-utero fractures before 20 weeks of gestation.[1,11] Although the mother of the index case had received ANC at a PHC facility, a prenatal scan was not done. Prenatal scans are not routinely done within public PHC facilities in the State but can be requested for and done at secondary health facilities.

Detection of fractures in-utero during routine prenatal scan should inform further evaluation and revision of the delivery plan.[11] Although there is no evidence to suggest better outcomes for prenatally-diagnosed cases of OI delivered via caesarean section as against SVD, hospital delivery and supervision by a skilled birth attendant provides a safer environment for essential care and timely referral for specialist care. Home delivery by the primiparous mother in this report, with supervision by an unskilled birth attendant, could have further predisposed the newborn to multiple fractures during delivery and made the phenotype appear more severe than what is obtainable for the particular genotype.

Moderate (common variable) OI may sometimes be difficult to clinically differentiate from severe progressively deforming OI at the initial stage. In-utero fractures can occur in both types but are more frequent in type 3. Severe short stature and cranial base abnormalities are commonly associated with both types 3 and 4 OI.[1,7] However, children with type 3 OI tend to have a triangular facie, bluish sclerae that clear over time and frequent fractures that heal with deformities, especially, when care is inadequate. On the other

hand, children with type 4 OI have fewer fractures that further reduce in frequency after puberty.[1]

Respiratory problems as highlighted in the index case are common manifestations of OI and are oftentimes, attributed to restriction of the chest cavity as a result of spinal deformities and rib fracture, impairing lung function. However, even mild cases of OI without significant chest wall deformities or fractures are also prone to respiratory complications. Experimental models suggest that the affectation of pulmonary fibroblasts in OI may play a significant role in lung inflammation, diminished lung compliance and other ensuing complications.[7] Pulmonary complications are a common cause of mortality in severe OI.

At times, child abuse and skeletal disorders, such as, achondroplasias, Achondrogenesis and Campomelic dysplasia may be clinically indistinguishable from OI and results of routine investigations may fall within normal limits. More specific investigations that reveal low procollagen type 1 propeptide levels in serum, high osteocyte levels and low bone turnover on bone histomorphometry and low bone mineral density (BMD) on dual-energy x-ray absorptiometry (DEXA) or quantitative CT scan support a diagnosis of OI. Definitive diagnosis is made by collagen synthesis analysis or DNA sequencing.[4,6] However, these specialized investigations are not widely accessible in resource constrained settings and may only be available in a few tertiary health facilities.[12,13]

The goals of management are to prevent fractures, deformities as well as other complications and promote independent ambulation and function. The management which can be broadly categorized into non-surgical and surgical interventions involves a multidisciplinary team approach and should be individualized based on the severity of affectation.

Bisphosphonates, such as Pamidronate, have been the mainstay of drug treatment for OI in Paediatrics and have been shown to improve bone mineral density, reduce bone fragility and slightly delay the progression of type 3 OI.[1,7] Other therapeutic agents such as, Sclerostin inhibitory antibody and Transforming Growth Factor beta (TGFβ) inhibitory antibody are being investigated with the hope of future use and better treatment outcomes in moderate to severe OI.[7] Research in the areas of gene therapy and cell transplantation are ongoing and there is evidence showing improvements in linear growth and bone mineral density, as well as, fewer fractures following bone marrow transplantation.

Orthopaedic surgery is indicated to treat fractures when closed reduction is not feasible and to correct skeletal deformities. The use of telescoping implants to stabilize bones is preferred in children with OI than static implants which they outgrow and predisposes them to more fractures and or more surgeries.[7] Postoperatively, gentle exercises help to prevent contractures and improve function.

Affected children should be gently handled and regularly turned from the neonatal period. Physical therapy should start early to help the infant achieve gross motor milestones like neck control and sitting, and it should be continued to improve muscle strength and function. Self-ambulation can be achieved with braces and crutches in moderate disease but those with severe OI may require wheelchairs.[1]

Genetic counselling may present a dilemma in resource constrained settings where molecular studies are not feasible but the updated classification of OI with genotype-phenotype correlation is quite helpful in counselling families in spite of the limitations. Prognosis depends on severity of the disorder in an individual and access to timely, supportive care. Children with type 2 OI usually die in infancy from cardiorespiratory complications while those with

milder forms of the disorder may live on into adulthood.[1] Ongoing psychosocial support should be provided for parents and affected children, especially, adolescents who struggle with issues of body image and low self-esteem.

Conclusion

In this case report, a combination of the clinical and radiologic features strongly suggested a type 3 osteogenesis imperfecta despite non-availability of confirmatory tests.

While the management of this form of OI may be quite challenging, especially, in low resource settings, concerted efforts through multidisciplinary team approach, psychosocial support and counselling is required to optimize the quality of life for affected individuals.

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Ethics: Ethical approval was obtained from the hospital Ethics committee and parental consent was given for publication.

Conflict of Interest: None

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