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CASE SERIES

Osteogenesis Imperfecta – A Case Series and review of recent advances in management

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Summary

Osteogenesis Imperfecta (OI) is an uncommon congenital abnormality of the connective tissues in which diagnosis and management pose significant challenges especially in Low and Middle-Income Countries. The objective of this report is to draw attention to this uncommon congenital anomaly. Two cases of OI were seen at birth and managed in Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria. One of the babies died shortly after birth while the other baby was managed and discharged home. The discharged baby was on follow-up care in the clinic until the parents defaulted from further care. She eventually died at home after series of hospitalisations for recurrent respiratory tract infections. In conclusion, a high index of suspicion is required during prenatal care visit. When detected at birth, parents are to be educated on the multidisciplinary approach to management, challenges and possible outcome as there is yet no cure for this condition.

Keywords: Osteogenesis Imperfecta, Prenatal Diagnosis, Multiple fractures, Skeletal diseases.

Introduction

Osteogenesis Imperfecta (OI), also known as Brittle bone disease, is a connective tissue disorder characterised by increased bone fragility as a result of abnormal collagen within the bone matrix, blue sclera and short stature. [1-3] It is the most common genetic cause of osteoporosis. [3] OI may also be associated with hearing loss and dentinogenesis imperfecta. The defects responsible for OI are directly related to Type I collagen and the defects include abnormalities of collagen primary structure and insufficient protein quantity, post-translational modification, folding, intracellular transport or matrix incorporation.

OI was initially classified into four types by Sillence in 1979, based on clinical and radiographic features; however, additional types have been proposed based on histologic findings. [3] Autosomal dominant OI is caused by mutations that alter the structure or quantity of type I collagen leading to a skeletal phenotype that ranges from subclinical to lethal. The recessive OI is caused by the deficiency of proteins that interact with collagen, thereby affecting its post-translational modification or folding. [1] The incidence of OI is about 1 in 20,000 to 50,000 live births in developed countries. [2,3] The mild form is usually under-diagnosed. Hence, the actual incidence may be higher. The

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incidence appears to be similar worldwide, but an increased rate has been observed in two major tribal groups in Zimbabwe. [4] OI has no sex predilection. Inheritance in the autosomal dominant forms occurs in all races while the recessive form is seen mainly among ethnic groups with consanguineous marriages. [3]

The importance of OI lies in the fact that it causes perinatal deaths or permanent physical handicap. [5] The diagnosis can be made clinically based on the appearance of the affected infant and the radiological findings. The confirmation of the clinical suspicion involves biochemical studies using cultured dermal fibroblasts from skin biopsy or tissue obtained from chorionic villous biopsy showing over-modified collagen on electrophoresis.[3] There is no cure for OI presently, and the management is mainly supportive and multidisciplinary in nature. The complications of OI include recurrent pneumonia which is a common cause of death in the paediatric age groups. Respiratory insufficiency, brainstem compression from basilar invagination, cerebral haemorrhage following birth trauma as well as hydrocephalus may also occur. [3]

Two cases of OI managed in a tertiary institution in Nigeria are described in this case series to create awareness about this rare congenital skeletal anomaly and also to highlight the challenges encountered in diagnosing and managing the cases. Approval was obtained from the Research and Ethics Committee of the hospital and consent was obtained from the parents of the two to use their clinical details.

Case Description

Case 1

Baby A, a female infant was admitted following delivery by emergency caesarean section in the Obstetrics unit of the Ekiti State University Teaching Hospital, Ado-Ekiti, on account of unplanned breech presentation in labour at 37weeks gestation. The mother was a 28-year old Para1^{+2} who received antenatal care at a primary health centre. The prenatal period was not adversely eventful, and she was referred from the primary health centre on account of malpresentation. The mother only took routine haematinic drugs during pregnancy. There was no history of ingestion of herbal concoction or any other medication in pregnancy. There was no known family history of skeletal anomaly or history suggestive of consanguinity between the parents.

The Apgar scores following delivery were 3, 5 and 7 at one, five and ten minutes of life respectively. The baby was small for age with a weight of 2.3kg and body length of 38cm. The baby was observed to be in respiratory distress, mildly pale, with normal temperature. The upper and lower limbs were short, deformed and curved medially. The occipitofrontal circumference was 32cm, which was below the third percentile for the age. She had sutural diastasis with wide anterior and posterior fontanelles, but the fontanelles were normotensive. The primitive reflexes were all depressed. The cardiovascular system and abdominal examination findings were normal. A clinical diagnosis of Osteogenesis Imperfecta was made.

The skull X-ray revealed defective ossification of the vault. (Figure 1) The babygram in Figure 2 shows multiple long bone fractures with multiple callus formation.

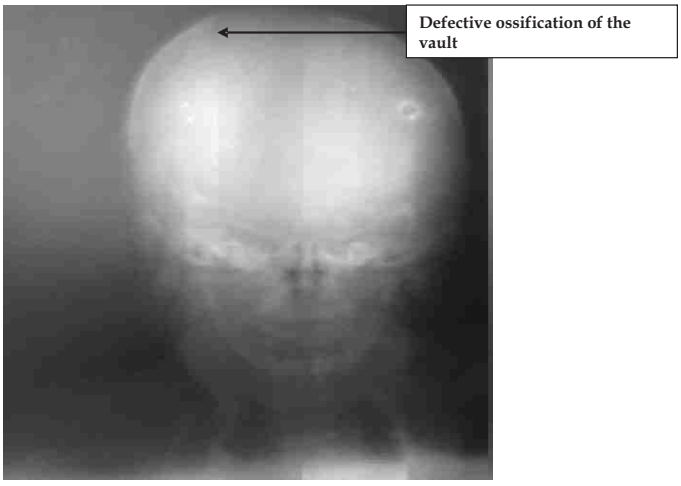

Figure 1: Plain Skull radiograph showing defective ossification of the vault in Case 1

The results of laboratory investigations included a Packed Cell Volume (PCV) of 37%. Alkaline phosphatase was 148 IU/L (normal for the age). The total and ionised serum calcium levels were also normal (2.7 and 1.4mmol/L) respectively. The serum electrolytes, urea and creatinine, the random blood sugar (RBS) as well as White Blood Cell count (WBC) were all within normal limits.

Full leg Plaster of Paris (POP) casts were applied bilaterally to correct the fractures noticed in the long limb bones following the resolution of asphyxia. She was subsequently discharged home on multivitamins, folic acid and calcium supplements on the 12th day of life. The POP casts were removed after clinical and radiological evidence of fracture union (the long bones of the extremities) in the third week of life. During follow-up in the clinic, she was noticed not to be thriving as she weighed 2.4kg in the seventh week of life despite exclusive breastfeeding. She had repeated admissions for respiratory tract infections and subsequently died at home in the third month of life.

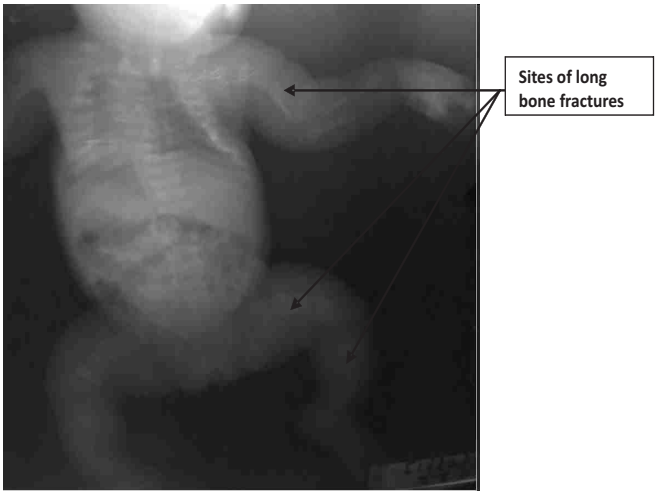

Figure 2: Babygram showing long bone fractures with evidence of fracture healing and callus formation in Case 1

Case 2

Baby J, a female, was delivered at 39 weeks and six days gestation following assisted breech delivery. The mother, a 32-year old Para 3^{+1} woman, presented in the hospital maternity unit at the second stage of labour following a referral e from a comprehensive health centre on account of breech presentation at term. There was no family history of skeletal abnormalities, but the mother had an unexplained stillbirth in the previous pregnancy. The antenatal period was without complication. The father was a 37-year old applicant. There was no history suggestive of consanguinity in both parents. The first child is alive and well. The index baby who was the third child of her parents was severely asphyxiated at birth with Apgar scores of 3, 4 and 7 at the first, fifth and tenth minute respectively.

Physical examination revealed a small-for-gestational-age baby, weighing 2.4kg, short with a body length of 40cm and her occipitofrontal circumference of 33cm. The body length and body weight were below the third percentile for the gestational age. She was mildly pale, in respiratory distress, had bluish sclera but normal temperature. Both the lower and upper limbs were short, deformed from multiple fractures and curved medially. The central nervous system examination revealed depressed neonatal reflexes, but the anterior, and posterior fontanelles were palpable, normotensive, soft and widened. There were no features suggestive of intraventricular haemorrhage in the baby. The cardiovascular and gastrointestinal systems were grossly normal. A clinical diagnosis of Osteogenesis Imperfecta was made.

The baby was admitted overnight but died within a few hours of admission hence some other investigations such as babygram and trans fontanelle ultrasound scan could not be carried out. The Packed Cell Volume was 36%, the Total White Blood Count was 27.2×10^{9}/L, and the random blood glucose was normal. The baby died before any intervention could be carried out. The parents declined post-mortem examination as well as a clinical picture of the baby.

Discussion

Making a diagnosis of Osteogenesis Imperfecta could be challenging in a low resource setting

where the required laboratory methods of diagnosis are not readily available. Therefore, clinicians are often constrained to rely solely on clinical and radiologic findings. [2] Where facilities are available, biochemical studies using cultured dermal fibroblasts from the skin biopsy or tissue obtained from the chorionic villous biopsy which shows over modified collagen on electrophoresis, can help in diagnosing the various types of OI, especially Types I to IV. [3]

The analysis of Type I collagen genes by DNA sequencing may be sufficient in making the diagnosis of OI such that a normal result diminishes the likelihood that the child has OI to well below 1%. These studies, when available, are usually unaffordable for most of the affected patients hence, our diagnoses in these cases were based on clinical and radiological findings as previously reported by some authors. [6] Apart from the short stature and the multiple fractures of the long bones with healing callus formation, the babygram also showed a fracture of the clavicle bilaterally and irregular rib outline with beading of the ribs. These features have been previously described in patients with OI. [6] The fractures in OI usually result from minimal trauma. [3] The multiple fractures observed in the two cases under review must have occurred *in-utero* since they were noticed at birth. These fractures are presumed to result from foetal movements *in-utero* or premature uterine contractions. [7] The battered baby syndrome is a close differential diagnosis of OI, but the index babies were born with the fractures. Abusive fractures seen in conditions like the battered baby syndrome are usually metaphyseal as against the global distribution seen in OI. [6]

OI can be diagnosed prenatally among at-risk pregnancies using obstetric ultrasound scan done in the early second trimester as early as the 16th week of gestation. [3] The antenatal ultrasound scan in the first baby was reported normal creating missed prenatal diagnosis of OI. This misdiagnosis may be due to the low expertise of the sonographer as the procedure was performed at a peripheral outlet before presenting at our hospital. Chorionic villous biopsy for biochemical and molecular studies can be done. [3] Prenatal diagnosis can improve the chances of survival in OI as the obstetrician is presented with an opportunity to plan the delivery with emphasis on minimal foetal manipulation at delivery. Also, it affords the paediatric team the chance to prepare adequately for the resuscitation and subsequent management of affected babies.

The lack of parental consanguinity in the two babies discussed may suggest sporadic OI (Type II or III in Sillence's classification) [8] which is due to "de novo" mutations in collagen I genes. In Nigeria and Ghana, 1.5% of unrelated individuals were found to be heterozygous carriers for a founder LEPRE1 mutation and about 0.4% of Mid-Atlantic African Americans also carry this mutation. [9] Homozygous children born to such carrier parents show an extremely severe/lethal perinatal form of OI (OI Type VIII) which is not clinically distinguishable from the sporadic Type II/III form. Therefore, these facts may explain the poor outcomes of the two cases reported.

The management of OI involves a multidisciplinary team that provides physical rehabilitation, dental care, neurological care, endocrine supports and surgical management. [1] Audiologic management may also be indicated for hearing deficits accompanying OI. New treatment methods such as cell therapy and new medications are currently undergoing trials. The medical treatment involves the use of biphosphonates which are anti-resorptive substances. The benefits of biphosphonate therapy include positive effects on bone histology such as increased trabecular number and cortical thickness and increased vertebral dual-energy X-ray absorptiometry (DXA) Z-scores. [10] The Receptor activator of nuclear factor – kappaB ligand (RANKL) inhibitors such as denosumab, which interfere with osteoclast formation, are currently undergoing trials to determine their usefulness in the management of patients with OI. [11] Human recombinant parathyroid hormone (Teriparatide) alone improved the bone mineral density and bone strength in some adults with the less severe OI. [12] Furthermore, Growth hormone has been

shown to improve linear growth in children with Types III or IV OI; it also resulted in positive changes in bone histology and vertebral DXA as well as muscle mass and strength. [13] Encouraging results are emerging from the trials using the combination of recombinant human growth hormone and biphosphonates. [14]

Molecular approaches to the treatment are also being explored using mesenchymal stem cells, whole bone marrow transplantation, ribozymes, antisense oligonucleotides and chemical chaperones with some reported promising results. [15-19] Despite all these advances and therapeutic trials, there is still no cure for OI. The management is mainly supportive. The surgical management of patients with OI involves osteotomies of long bones with the placement of intramedullary rods which is undertaken to correct deformities which impede functions and prevents the recurrence of fractures. Currently, surgeons have at their disposal, two types of telescoping rods—the Fassier–Duval telescopic intramedullary system and the Sheffield telescopic intramedullary rod. Unfortunately, rod migration is a commonly reported complication in the management of OI. [20]

Physical rehabilitation helps to maximise the patient's gross motor functions and daily life competencies. This is especially important in childhood, when the fundamentals of life functions are established, and for older individuals, who will experience combined effects of OI and ageing. The fractures in the patient who survived for few months were managed with Plaster of Paris casting alongside other medical conditions. This supports the widely held belief that, healing of fractures and bone remodelling in OI patients occur rapidly and non-union of fractures is rare in them. [2] However, stunting and limb deformities may become evident as the affected child grows older and this is not unconnected with the effects of multiple fractures and disorderly manner of bone healing. [2] The multiple fractures can also prevent ambulation in the child. [7]

Individuals with OI succumb to complications such as recurrent pneumonia which could be due to respiratory insufficiency. In addition, the accumulation of pulmonary secretions which in turn serve as culture media for bacteria to trigger more respiratory tract infections is key to the recurrent respiratory disorders in OI, thus, setting off a vicious cycle. Other complications of OI include neurologic disorders such as basilar invagination and consequent brainstem compression as well as hydrocephalus and cerebral haemorrhage following birth trauma. [3] Complications of anaesthesia are also common among individuals with OI who may, ironically, require surgical interventions.

Early diagnosis will improve the chances of survival of the affected child. This will ensure that appropriate counselling is done before delivery of the affected baby, the delivery will be planned and all the teams of experts required for the optimal care of the baby will have ample opportunities to prepare. This will go a long way in minimising morbidities.

Adequate education and counselling of the family is essential in the prevention of adverse psychological reaction to the birth of a baby with OI. In addition to uninterrupted access to appropriate medications, parents need special instructions on physical handling of the affected children in order to minimise the risk of new fractures while maintaining bonding and physical stimulation.

It is important to highlight that the scope of care received by the index babies was limited by the inadequacies of equipment, medications and other needed services in a low-resource setting. It is plausible that the unexplained stillbirth experienced by the mother of the second case, in her previous pregnancy, might have occurred as a result of OI. This further underscores the need for comprehensive genetic screening tests for the family to identify the risk of recurrence and make appropriate future childbearing plans which could improve the chances of a better outcome.

Conclusion

It is important to note that there is yet no cure for OI. The diagnosis and management can be challenging

in resource-poor settings like ours due to extreme reliance on clinico-radiological diagnosis in the absence of genetic and biochemical studies and lack of appropriate medications and optimal support services. Obstetricians should encourage prenatal diagnosis within the limits of the sonological services available. The paediatrician should also be involved in the planning of the delivery of the baby with OI to minimise perinatal morbidities. Active physical rehabilitation commenced early in life for the severe non-lethal types can allow some of the affected children attain a higher functional level. This highlights the need for early diagnosis and management of the affected patients.

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