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Osteogenesis Imperfecta Type II - Rare Lethal Disorder: A Case Report

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Abstract

Osteogenesis Imperfecta (OI) is a rare group of disorders with variable spectrum of clinical presentations as well as genetic presentation. It is characterized by excessive fragility of bones with recurrent fractures and low bone mass. It is caused mainly due to mutations in genes encoding for collagen. There are total 13 types of OI according to pattern of inheritance. On the basis of phenotypic presentation, it has been clinically classified under 4 categories. We have reported a rare case of Osteogenesis imperfecta type II with autosomal recessive pattern of inheritance which is also rare. The baby was born at Sanjay Gandhi Memorial Hospital, Mangolpuri, Delhi, India. The detailed discussion is being presented in the case report. Diagnosis of OI type II was based on clinical features and findings of Infantogram. The treatment of OI includes involvement of multiple modalities like medical and surgical interventions. Management of OI requires extensive alertness especially in prompt diagnosis. Newer treatment modalities are now being tried and researched upon to reduce the associated morbidity and mortality.

Keywords: Osteogenesis type II; Autosomal recessive inheritance; Rare and Lethal

Introduction

Term Osteogenesis Imperfecta (OI) was coined by Lobstein in 1835 [1]. OI represents a group of rare inherited disorder related to connective tissue which is characterized by recurrent fractures, low bone mass, excessive fragility of bones. It is caused due to mutation in genes coding for collagen [2,3]. The overall incidence of Osteogenesis imperfecta is 1 in 20000 live births with that of type II as 1:60,000 live births [1,4].

The most commonly known autosomal dominant forms results mostly in mutations of *COL1A1* and *COL1A2* genes which constitutes about >90% of cases [5]. But since last decade, autosomal recessive forms have been identified due to advanced molecular technologies and a total of 150 mutations are now known [2,6].

As per 2009, INCDS (International Nomenclature Group for Constitutional Disorders of the Skeleton) classification, the OI syndromes were classified in 5 phenotypic categories giving each category an Arabic numeral indicating unique phenotypic description. There were total 13 types i.e. I-XIII out of which type I to V belongs to autosomal dominant form and rest were kept in autosomal recessive form [7]. Individuals having OI forms V to IX have been found to have mutations in genes like *CRTAP*, *LEPRE1*, *PPIB*, *FKBP10* [6]. According to Clinical classification by Silence et al. [6] proposed in 1979, OI was classified under 4 types and is the most helpful classification system for prognosis and genetic counseling [6]. Rabiee and Etemadi in 2011 described Type I as most common and mildest of all forms [1].

Osteogenesis imperfecta is characterized by multiple & recurrent fractures that can be intrauterine, perinatal or postnatal. Other noticeable features include blue sclera, otosclerosis with hearing loss, high arched palate, hyperlaxity of ligaments and skin, defective dentition (dentinogenesis imperfecta), scoliosis and growth retardation [2].

The diagnosis of OI is made clinically. Radiographic support and collagen analysis of skin contribute in confirmation [2]. Prenatal Ultrasonography is most helpful in evaluation and capable of detection of limb length abnormality at 15 to 18 weeks of gestation. Mild OI forms may have normal USG findings [2]. Three Dimensional (3D) ultrasonography is considered superior in diagnosis as compared to 2D sonography as it provides multiple modes for better visualization and

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reconstruction of images [8,9].

Treatment in such cases involves different modalities like medical, surgical interventions, physical and experimental therapies. Management of fractures can be done by placement of intramedullary rods [7]. Medical treatment includes Bisphosphonate therapy, Injection pamidronate, Injection Zoledronic acid, maintenance therapy with calcium and vitamin D. Genetic counseling and family screening should be offered [10].

Case Presentation

We report a preterm (33 weeks) male neonate delivered to primi mother by normal vaginal delivery at our hospital with delayed cry. Baby was resuscitated and shifted to NICU in view of birth asphyxia & respiratory distress with multiple swellings over bilateral upper and lower limbs.

His mother received routine ante natal care and pregnancy was uneventful. Only routine supplemental drugs such as iron folic acid and calcium was taken. Ante natal USGs were reported normal.

On examination, he was lying in 'frog- like position' with multiple swellings over bilateral upper and lower limbs. Respiratory distress was present in the form of tachypnea and increased work of breathing, for which he was put on CPAP support. He has associated grayish blue sclera with high arched palate. A diagnosis of osteogenesis imperfecta type II with severe birth asphyxia was made. Infantogram was done which was reported to have multiple fractures incurred in utero at various stages of healing involving multiple ribs bilaterally, both humeri, radii and ulnae, femora, tibia and fibulae with thin cortices and resultant cystic changes. Treatment given was mainly supportive in the form of CPAP support, intravenous fluid, intravenous antibiotics. But despite all the efforts, baby's condition continued to deteriorate and he died after 4 h of birth (Figure 1).

Discussion and Literature Review

OI is rare disorder and it was termed as "osteopsathyrosis idiopathica" by Lobstein. Vronik coined the current terminology in 1845. Silence et al. clinical classification is most widely accepted and classifies OI in 4 types - Type I - dominantly inherited OI with blue sclera; Type II - OI with autosomal dominant pattern of inheritance with perinatally lethal deformity with crumpled femora; Type III - Progressively deforming most OI with no scleral abnormality and autosomal dominant inheritance and Type IV - autosomal dominant inherited OI with no scleral findings [2].

In Indian population, the bluish grey color of sclera is due to thinness of the collagen layers of sclera that allows underlying choroid layers to be seen. Type II produces brittle bones that are lethal in utero or shortly after birth [1].

Cundy in 2012 described "Dentinogenesis imperfecta" as another associated feature in which teeth may have characteristic amber, yellowish brown or translucent bluish gray color because of deficiency of dentin that is rich in type 1 collagen. Lo Mauro et al. in their study showed respiratory complications secondary to chest deformity and scoliosis leading to thoracic functional limitations and is the leading cause of death in most patients of OI [1].

Diagnosis of type II OI in our patient was based on multiple fractures at birth, grayish blue sclera and supportive radiological evidence. No positive history suggestive of OI and other skeletal deformities was found in any of family members. Akiode et al. in

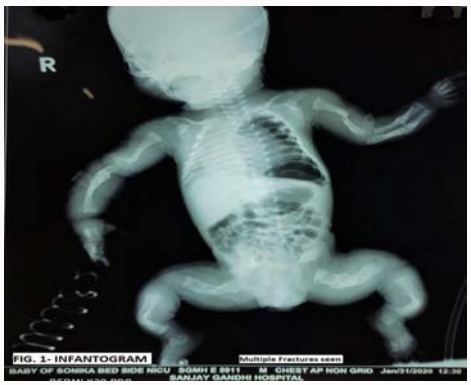

Figure 1: Infantogram.

Sagamu and Akinola et al. in Lagos in West Nigeria reported similar cases and diagnosed on basis of similar clinical features [2].

Prenatal diagnosis by fetal USG is possible but no abnormality was detected during any antenatal 2-dimensional USG in our patient. Multiple fractures can occur during delivery or with minimal stress but there is no data is available supporting the fact of improved outcome with caesarean section [2]. In comparison to 2D ultrasonography, 3D ultrasound helps in comprehensive and more complete detailed illustrations of skeletal dysplasia due to various reconstruction modes available. Benoit et al. and Garjian et al. in their study reported 3D ultrasonography more superior to conventional 2D technique in skeletal system and fetal neural axis evaluation [8]. Also according to comparative study done by Ayadi et al. [9]. Three Dimensional (3D) ultrasonography improves accuracy of the prenatal diagnosis of skeletal disorders.

New therapeutic approaches are now being worked at in the form of anti-sclerostin antibody, cathepsin K antibody, Transforming growth factor B and prenatal & post natal transplantation of mesenchymal stem cells [6]. Strontium ranelate and denosumab targeting RANKL pathway are also being studied for their therapeutic role in therapy for OI [7].

Conclusion

OI is a rare inherited group of disorders which is mostly autosomal dominant but autosomal recessive forms are being now studied extensively. We report this rare case of OI type II on basis of clinical features described and findings of infantogram confirming it. Pattern of inheritance is most likely to be autosomal recessive since there was no positive family history which is rare pattern of inheritance for OI type II. All the antenatal ultrasounds were reported normal. This can be attributed to 2D ultrasonography used in our patient in ante natal period which is an inferior modality in comparison to 3D ultrasonography for detection of skeletal deformities. Hence, any suspected skeletal deformity case or cases with positive family history should be screened with 3D ultrasonography during antenatal period, wherever possible, to have better chances of detection. No substantial data is available for supporting cesarean section as better modality for conducting delivery with suspected OI but the associated risk of increased chances of fractures in intrapartum period during vaginal delivery specifically in OI type II demands for further extensive research in this area to improve the outcome of deliveries. This case report and other similar reports demand for extensive alertness in identifying and diagnosis of such cases which would help in further management. Newer treatment modalities to be researched to reduce

the morbidity and mortality associated.

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