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OSTEOGENESIS IMPERFECTA TYPE 11: CASE REPORT

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Abstract

Background: Osteogenesis imperfecta (OI) is a genetic condition distinguished by heightened bone fragility and reduced bone density. OI not only lead to low trabecular bone mineral density and thin cortices, but also results in small, slender bones. **Objective:** Early diagnosis of osteogenesis imperfecta when other family members have undiagnosed skeletal deformity. **Case report:** B/O K, inborn female baby born by vaginal delivery to 3rd degree consanguineous parents ,G2P1D1 mother at 35weeks +2 days of gestation with birth weight of 2.3 kg. Anomaly scan done was normal. Baby was discharged on day 12 of life with diagnosis of Transient tachypnea of newborn and neonatal jaundice. Previous sibling was female, delivered preterm at 28 weeks of gestation with birth weight 1.2 kg by vaginal delivery at PHC. Antenatal scans were normal. Baby was referred to tertiary care hospital at 2 hrs of life for birth asphyxia. Baby died on day 5 of life while on ventilator support. At 36 days of life ,baby was brought to emergency department with complaints of decreased movement of left upper limb for past 1 day. There was no history of trauma. On examination baby had tenderness and restriction of movement of left upper arm. Ophthal evaluation done was normal. X ray taken showed a fracture in shaft of left humerus. Orthopedic opinion was taken and baby was managed conservatively with analgesics and restriction of movement of left arm. Clinical exome sequencing was sent with clinical suspicion of Osteogenesis Imperfecta Type 11. **Results:** Clinical exom sequencing was suggestive of ostegenesis imperfecta type 11 involving FKBP 10 gene . When baby came for follow-up at 62 days of life, the range of movement of left upper arm had improved, swelling in left arm was present. Baby had weight gain . Bisphosphonates with greater potency such as zoledronic acid is planned to be started at follow up at 6 months of age. **Conclusion:** The management of OI involves multidisciplinary approach which includes neonatal orthopaedic, physiotherapy and rehabilitation specialities. Early diagnosis helps in improving the course of the disease.

Keywords: Osteogenesis Imperfecta, Osteogenesis Imperfecta Type 11, Fracture, Neonate, Clinical Exom Sequencing, FKBP 10 Gene.

INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic condition distinguished by heightened bone fragility and reduced bone density. In this case we aimed at arriving at diagnosis as other family members were affected and the newborn baby started showing symptoms.

Pathophysiology

Changes in collagen type I molecules result in modifications to the structure of the bone. The bone from OI patients has a higher average mineral density than age matched controls and the abnormal collagen may have lower tensile strength . This may lead to the brittleness of the bones in OI. OI not only lead to low trabecular bone mineral density and thin cortices, but also results in small, slender bones. Together these factors contribute to the fragility of the bones.

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Case report

B/o K, female baby born by Normal delivery to 3rd degree consanguineous parents ,G2P1D1 mother at 35wks +2 days of gestation with birth weight of 2.3kg at SMCH. Anomaly scan done was normal.

Previous sibling was female delivered preterm at 28 weeks of gestation with birth weight 1.2 kg by nvd at primary Health Center. Antenatal scan were normal. Baby was referred to Chengalpattu GH at 2 hrs of life for birth asphyxia. Baby died on day 5 of life while on ventilator support.

Baby cried soon after birth . Baby was shifted NICU for respiratory distress and was started on NIV support. Respiratory distress settled over the next 1 day. Feeding was initiated through orogastric tube initially and progressed to DBF. Peak SBR on day 4 of life was 18.95mg/dL and was treated with phototherapy. Baby was gaining weight well with no post-natal issues. Baby discharged on day 12 of life.

At 36 days of life,baby was brought to emergency department with complaints of decreased movement of left upper limb for past 1 day. There was no history of trauma. On examination baby had tenderness and restriction of movement of left upper arm(figure 1).Ophthal evaluation done was normal (figure 2). X ray taken showed a fracture in shaft of left humerus(figure 3). Other limbs were examined and fractures ruled out. Orthopedic opinion was taken and baby was managed conservatively with analgesics and restriction of movement of left arm. Brachial plexus injury was ruled out.Detailed history revealed other family members (paternal uncle and aunt) had undetected bony deformity since birth(figure 4). In view of consanguineous marriage, significant family history osteogenesis imperfect was suspected. Clinical exome sequencing was sent with clinical suspicion of Osteogenesis imperfecta. Clinical exome sequencing was suggestive of ostegenesis imperfecta type 11 involving FKBP 10 gene (figure 5).

When baby came for follow-up at 62 days of life, the range of movement of left upper arm had improved, swelling in left arm was present (figure 6). Baby had weight gain. It is planned to start inj Zoledronic acid at 6 months of life. In the follow up it is planned to start inj Zoledronic acid at 6 months of life. Length monitoring to be done. Proper handling of the infant is adviced like while changing diaper a hand to be placed behind the buttock region.

Figure 1: Ophthal Evaluation

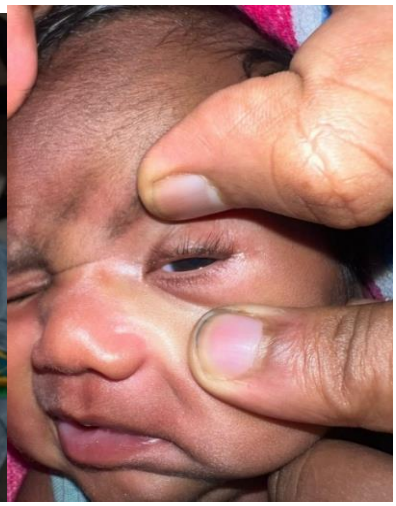

Figure 2: Swelling in Upper Arm

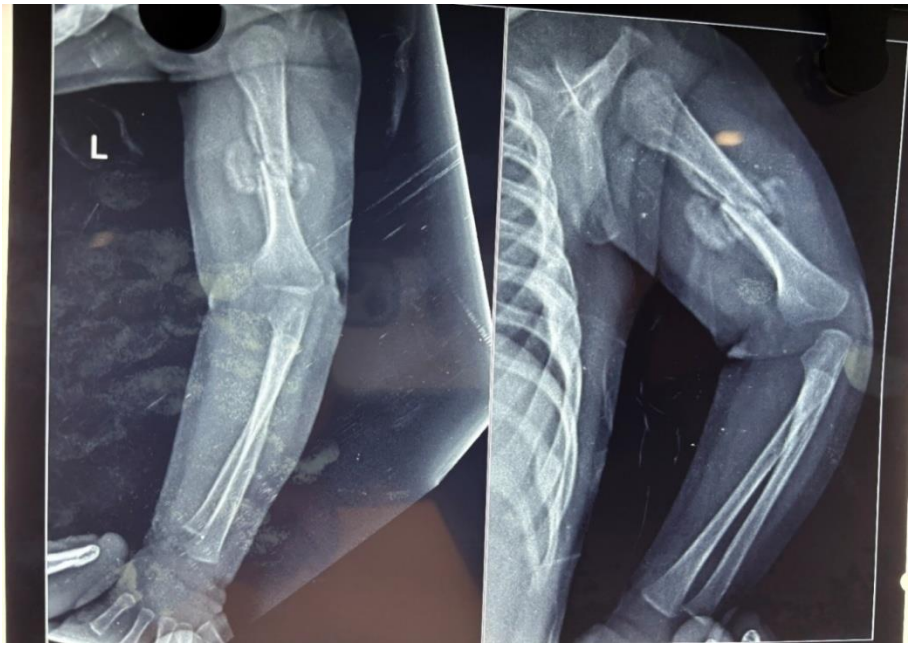

Figure 3: Xray Humerus after Diagnosis

Figure 4: Family Members Affected with Bony Deformities

DISCUSSION

OI type XI is an autosomal recessive form of OI. The FKBP10 gene encodes a chaperone that participates in type I procollagen folding, and determined that FKBP10 mutations affect type I procollagen secretion(1).

The management of OI involves multidisciplinary approach which includes neonatal orthopaedic, physiotherapy and rehabilitation specialities.

The gene FKBP10 produces FKBP65, a chaperone protein crucial for proper cellular function. Mutations in FKBP10 can result in Bruck syndrome(BS) type 1, characterized by congenital joint contractures and varying degrees of bone fragility. In some cases, FKBP10 mutations lead to a severe form of Osteogenesis Imperfecta (OI) without joint

contractures(2) Despite seemingly normal collagen structure, there are alterations in collagen stability, resulting in accumulation of procollagen aggregates within the endoplasmic reticulum (ER). These alterations also impact intermolecular collagen linkage, akin to patients with mutations in PLOD2. This similarity suggests a functional interplay between FKBP10 and PLOD2, influencing collagen stability and cellular integrity. Understanding the functional relationship between FKBP10 and PLOD2 could provide insights into the mechanisms underlying collagen-related disorders, facilitating the development of targeted therapies for conditions like Bruck syndrome and OI. The phenotypic spectrum of FKBP10 mutations encompasses OI alone, OI with contractures (BS), and a congenital contracture syndrome

In future pregnancy of this parent, chorionic villous sampling or amniocentesis for genetic analysis of FKBP gene is planned. For next pregnancy caesarean delivery is not necessarily indicated as Cubert et al found caesarean delivery did not decrease the fracture rate at birth (5)

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
***FKBP10* (+)** (ENST00000321562.9)	Exon 2	c.344G>A **(p.Arg115Gln)**	Homozygous	Osteogenesis imperfecta, type XI (OMIM#610968)	Autosomal recessive	Likely Pathogenic **(PM1,PM2,PP3,PP5)**

Figure 5: Clinical Exome Sequencing Result

Figure 6: Baby on follow up

Medical Management

Bisphosphonates have potent anti-resorptive properties and inhibit osteoclast function(3). Although the quality of the new bone that is formed remains unchanged, the bones benefit from greater mechanical strength due to overall increased bone mass. Traditionally intravenous pamidronate has been used in children, however newer bisphosphonates with greater potency such as zoledronic acid have started to be used in clinical practice.With the development of stem cell therapy, there is a growing possibility that the treatment of OI could be started during pregnancy.

CONCLUSION

The management of OI involves multidisciplinary approach which includes neonatal orthopaedic, physiotherapy and rehabilitation specialities. Early diagnosis helps in improving the course of the disease.

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