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PRENATAL EXCLUSION OF IFITM 5 GENE RELATED OSTEOGENESIS IMPERFECTA TYPE V BY MUTATION ANALYSIS; A RARE CASE

Gynecology

Vandana Bansal Fetal Medicine Center, Nowrosjee Wadia Maternity Hospital, Mumbai, Maharashtra, India

Neha Singh* Fetal Medicine Center, Nowrosjee Wadia Maternity Hospital, Mumbai, Maharashtra, India *Corresponding Author

Vasundhara S. Chennuri Centre for Medical Genetics, Mumbai, Maharashtra, India

ABSTRACT

This case presents an approach to genetic counselling and prenatal diagnosis for a very rare subtype of osteogenesis imperfecta (type V) along with challenges in identification of molecular aetiology and prenatal exclusion of genetic disease with genetic heterogeneity. A 24-year-old, primigravid woman was referred for genetic counselling in the first trimester for husband and his first-degree relatives manifesting features of osteogenesis imperfecta (OI). The husband had multiple fractures since childhood and was wheel chair bound. On pedigree analysis, the mode of inheritance noted in the family was autosomal dominant. Clinical exome covering 6400 genes was performed for the husband which identified heterozygosity for known pathogenic mutation c.-14C>T in IFITM5 gene (OI type V) and variants of uncertain significance (likely pathogenic) c.1870C>T (p. P624S) and c.2330G>A (p. R777H) gene in COL1A2 gene (OI type I). Chorionic villous sampling was done at 13 weeks of gestation. Foetus was heterozygous for the two variants of COL1A2 gene but negative for pathogenic variant in IFITM5 gene. Extended family analysis linked the IFITM5 allele to disease whereas COL1A2 variants were also present in a clinically un-affected paternal aunt suggesting them as possibly benign variants. After mutation analysis of unaffected and affected relatives of husband, it was concluded that variants of COL1A2 gene seen in the fetus, are unlikely to affect foetus from OI as they did not cause disease in the unaffected relative. Pregnancy was continued till term. All antenatal ultrasound findings were normal. She delivered a healthy male child at term. Postnatal course of baby was uneventful with a normal infantogram. This case report highlights the importance of proper genetic evaluation of proband and extended family members by molecular diagnosis and multidisciplinary approach while dealing with such rare genetic disorder for prenatal diagnosis in fetus to improve perinatal outcome by exclusion of disease.

KEYWORDS

Osteogenesis Imperfecta type V, prenatal diagnosis, IFITM 5 gene, COL1A2 gene, autosomal dominant, chorionic villous sampling.

INTRODUCTION

Osteogenesis Imperfecta, also known as Brittle Bone disease, is an inherited connective tissue disorder characterized by increased bone fragility, recurrent fractures, blue sclerae, impaired hearing, defective dentition, and skeletal deformities. It is evident from review of literature that there is a wide variability in phenotypic expression and severity of disease along with genetic heterogeneity among affected population ranging from perinatal lethal to subtle fracture susceptibility or generalized osteopenia.

Sillence et al (1979) classically described four distinct groups of OI based on his observations of an epidemiological and genetic study done on Australian population [1]. Later, Glorieux et al (2000) proposed a new entity of OI i.e. OI type V because of its distinctive clinical, histological, and molecular characteristics from other forms [2]. Both autosomal dominant and autosomal recessive forms are known. There are currently seventeen types of OI listed in Online Mendelian Inheritance in Man (OMIM).

Osteogenesis Imperfecta (OI) type V (OMIM 610967) is a novel rare autosomal dominant form of OI which is moderately deforming and progressive disease resulting in moderate to severe bone fragility of long bones and vertebral bodies. It is characterized by calcification of the forearm interosseous membrane, hyperplastic callus formation, radial head dislocation and subphyseal metaphyseal radiodense line, in the absence of blue sclera and dentinogenesis imperfecta [3]. Cho et al (2012) identified a heterozygous mutation of c.-14C>T in the 5'-untranslated region of a gene encoding Interferon-induced transmembrane protein 5 (IFITM5) on chromosome 11p15 after linkage analysis and whole exome sequencing, as the causative mutation involved in OI type V [4]. This is in contrast with other common forms of OI where mutation involves one of the two genes, namely, COL1A1 & COL1A2.

Several cases of prenatal diagnosis of OI based on ultrasound findings have been reported in literature. But, ultrasound based prenatal diagnosis is useful only for detection or exclusion of lethal and severe forms like type II and type III [5,6].

To our knowledge, this is the first case of prenatal exclusion of OI type V where affected father was detected to have OI type V after genetic evaluation by molecular diagnostic testing and genetic counselling was sought by the pregnant couple in first trimester of pregnancy.

CASE PRESENTATION

A 24-year-old, primigravid woman was referred for genetic counselling in first trimester at 7weeks for husband manifesting features of osteogenesis imperfecta (OI). Couple were non-consanguineous. Pedigree analysis was done (figure 1) and similar disease was noted in two family members (husband's father and brother). The husband was 40 years old and suffered the first fracture on day 1 of life. Thereafter, fracture recurrences occurred almost every 2-3 months, till 18 years of age, after which none were noticed. The sclerae were normal. Teeth were normal. He was short with spine showing lumbar scoliosis. He was wheel chair bound. He did not receive bisphosphonate therapy. His brother had similar history and phenotype. The father had a milder course of disease with first fracture being noticed around 5-6 years of life. Skeletal radiographs showed generalised osteopenia, thin ribs and scapular and pelvis hypoplasia characteristic features of OI. The fracture sites showed hyperplastic callus formation. The forearm x rays showed bone growth between the radius and ulna (calcified interosseous membrane) which limited the pronation and supination movements (figure 2).

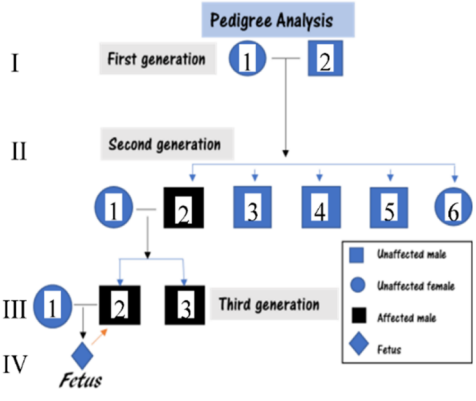


Figure 1Pedigree analysis

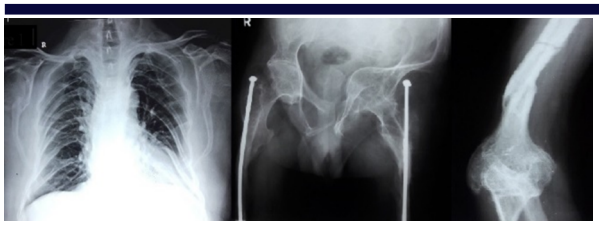


Figure 2 Skeletal radiographs showing bell shaped thorax, thin wavy ribs, pelvic and acetabular deformity with intramedullary steel rods in situ, fracture humerus with hyperplastic callus

Molecular diagnostic testing (by Sanger sequencing) of husband revealed presence of three heterozygous mutations involving c.-14C>T in *5′ UTR of the IFITM5 gene (pathogenic) and c.1870C>T in exon 32 & c.2330G>A in exon 38 of COL1A2 gene (likely pathogenic with probable damaging effect)*. Chorionic villous sampling was done at 13 weeks of gestation. Foetus was found to be heterozygous for the two variants of COL1A2 gene which could be likely pathogenic but negative for pathogenic variant in IFITM5 gene. Figure 3 presents sanger sequencing data (electropherogram) from the fetus.

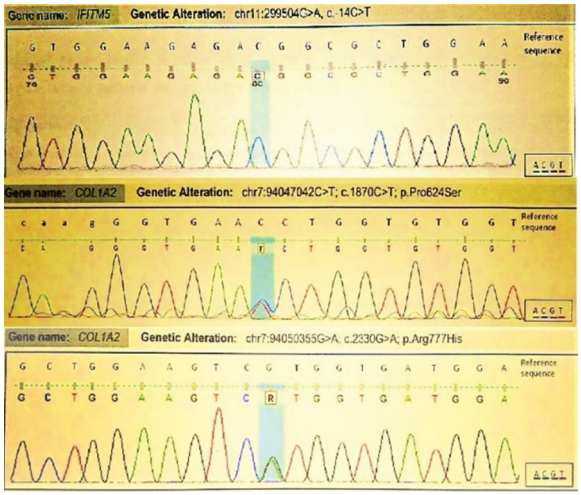


Figure 3 Sanger sequencing data (Electropherogram) from the fetus showing the reference nucleotide 'C' at position c.-14 in the IFITM5 gene and two heterozygous nucleotide changes 'C>T' at position c.1870 & 'G>A' at position c.2330 in the COL1A2 gene.

In view of inconclusive molecular diagnosis in foetus and unknown pathogenicity of two variants in COL1A2 gene, husband's affected father and brother and an unaffected paternal aunt were also tested for same gene variants. Affected members were found to be heterozygous for pathogenic mutation in IFITM5 gene as well as for the other two variants in COL1A2 gene like husband. Therefore, it was concluded that they had *IFITM5 gene related Osteogenesis Imperfecta Type V*. However, the pathogenicity of COL1A2 gene variants remained unproven. The unaffected paternal aunt did not show the familial pathogenic mutation in IFITM5 but had presence of COL1A2 gene variants similar to the foetus. Table 1 shows the genotype-phenotype correlation of OI and COL1A2 & IFITM5 genes in the family.

Table 1: Genotype - phenotype correlation of OI and COL1A2 & IFITM5 genes in the family

Gene	Variant	Genotype of Proband (affected Husband) (III-2)	Genotype of proband's father (affected) (II-2)	Genotype of proband's brother (affected) (III-3)	Genotype of proband's paternal aunt (unaffected) (II-6)	Genotype of fetus (IV-1)
COL1A2	NM_000089: exon32: c.C1870T: p.P624S	Het	Het	Het	Het	Het
COL1A2	NM_000089: exon38: c.G2330A: p.R777H	Het	Het	Het	Het	Het
IFITM5	NM_001025295.2: c.-14C>T	Het	Het	Het	**Absent**	**Absent**

Het: Heterozygous

Genetic expert's opinion was taken and after interpretation of genetic testing results, it was concluded that foetus is unlikely to be affected from IFITM5 gene related OI type V and other two variants of COL1A2 gene are unlikely to affect foetus from OI as they did not cause disease in unaffected relative. Pregnancy was continued till term. All antenatal ultrasound findings were normal. She delivered a healthy male child at term. Postnatal course of baby was uneventful with a normal infantogram shown in figure 4.



Figure 4 Infantogram of new born showing no bone fractures

DISCUSSION

Osteogenesis Imperfecta is an inherited connective tissue disorder with commoner mode of inheritance being autosomal dominant caused by mutations in one of the two genes namely *COL1A1* and *COL1A2* in most instances. Diagnosis of OI is suspected during fetal life, at birth, postnatally or later in adulthood. In all suspected cases, first line of evaluation includes detailed medical history, family history, physical examination, radiography and routine investigation followed by genetic evaluation. There is 50% risk for OI in the sibling when either parents have OI. Prenatal Ultrasound should be offered as early as 13-14 weeks gestation for severe, lethal form of OI (OI type II) and 16-20 weeks for OI type III in all pregnant women at risk of OI. Detection of skeletal anomalies (like micromelia and undermineralization of bones) on ultrasound may raise the suspicion of OI with major differential diagnoses being OI type II, achondrogenesis type IA, IB and II, and autosomal recessive (severe infantile) hypophosphatasia [6].

Ultrasound findings in cases of OI II and III include undermineralized skull and bones, short limbs, thin beaded ribs, angulation or bowing and fractures of long bones and deformable calvarium before 20 weeks and long bone bowing and/or fractures after 20 weeks, rarely in cases of OI IV and I. However, in cases of OI V, no specific ultrasound findings have been described in literature till date. However, anomaly scan at 18-20 weeks' gestation may not always rule out OI.

Arundel et al reported first case of evolution of radiographic appearance of long bones in an infant with type V OI where mother was detected with OI V 9 years prior to pregnancy and antenatal ultrasound at 24 weeks' gestation revealed short long bones with splayed ends, bowing of few long bones, femoral fracture and fibular fracture at 33 weeks' and postnatal radiograph on day one of life showed a bell shaped chest with thin and gracile ribs, multiple rib fractures, both acute and healing, and flaring at anterior rib ends [7].

Navarro et al described two mutations in IFITM5 gene causing distinct forms of OI in two patients and limb shortening diagnosed prenatally in one of them [8].

Recently, Hoyer-Kuhn et al identified a nonclassical heterozygous mutation in IFITM5 gene located in coding region which resulted in severe OI with prenatal onset (bowing and shortening of lower limbs) and extreme short stature. Therefore, they emphasized that the entire gene-not only the 5'-UTR harboring the classical OI type V mutation-has to be analyzed to exclude the causal role of IFITM5 [9].

Raghunath et al described a method of early prenatal diagnosis of collagen disorders including OI by direct biochemical analysis of

chorionic villous biopsy samples which allows better identification of molecular defects from extracted collagens. Results are available within 3-5 days after biopsy. They correctly predicted a healthy fetus and affected embryo with lethal OI in consecutive pregnancies in which asymptomatic mother was a somatic mosaic for a COL1A1 G-to-A transition [10]. It can be offered only when collagen screening studies have been completed in affected parent or previous affected child, to pregnant women at risk for OI type II, III or IV [6]. However, role of biochemical testing in case of OI type V is not defined yet.

Mutation analysis using DNA extracted from CVS cells or amniocytes, can be performed for all types of OI, if mutation is known in the family members. This method is most commonly used for early and accurate prenatal diagnosis of OI [6].

CONCLUSION

It can be concluded that multidisciplinary approach in solving such rare and challenging cases is the key towards managing these pregnancies successfully by providing couple with an appropriate and correct prenatal diagnosis and prognostication. Prenatal diagnosis in such cases can result in significant reduction in perinatal morbidity and mortality and subsequent morbidity and handicap later in life. Therefore, proper workup of index case is essential for making prenatal diagnosis of such rare genetic disorders.

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CONFLICTS OF INTEREST

Authors declare that they have no conflict of interest relevant to this article.

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