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Prenatal Assessment of Three Rare Syndromes from Telangana Region by 3D/4D Sonography

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Abstract

Ultrasound imaging serves as a powerful tool in the diagnosis of fetal anomalies. The three and four dimensional ultrasound scan overcomes some of the key limitations related to two-dimensional imaging. It facilitates detailed evaluation of suspected fetal abnormalities of face, neural tube, heart, skeletal and many subtle birth defects, which is pertinent to the pediatric surgeon for timely intervention. It also determines the age and developmental stage of the fetus, detects location and abnormalities of placenta, spot abnormal bleeding, ectopic pregnancies. The present article describes the three rare syndromes Meckel Gruber Syndrome, Holt Oram Syndrome (HOS) and Emanuel syndrome identified. During an attempt to screen a total of 3000 high risk pregnant women for the presence of congenital anomalies by 3D/4D sonography prenatally. Disruption of genes due to deletions and translocation are also identified which could be the putative candidate genes in the syndrome onset.

Keywords: Ultrasound; Three-dimensional; Four-dimensional; Fetal anomalies

Abbreviations: MGS: Meckel Gruber Syndrome; HOS: Holt Oram Syndrome; ES: Emanuel syndrome, FISH: Fluorescence *In Situ* Hybridization, LV: Left Ventricle, VSD: Ventricular Septal Defect, PDA: Patent Ductus Arteriosus, 2D ECHO: Two Dimensional Echocardiogram

Introduction

A pregnancy is high-risk or complicated when the life or health of the mother or baby may be at risk. The chances of having an abnormal child with anomalies had been reduced to a greater extent by implementing ultrasonogram in the routine clinical practice. Ultrasound has been used as imaging tool in limited medical practice for more than three decades and had proved useful in the diagnosis of fetal anomalies. The recent advent of 3- and 4-dimensional ultrasonography has facilitated detailed evaluation of suspected fetal abnormalities such as facial anomalies, neural tube defects, heart defects and skeletal malformations, which is pertinent to the pediatric surgeon for timely intervention. Four dimensional ultrasound scan creates a live action images of the unborn child and can determine the age of the fetus, the developmental stage of the fetus, detect uterine placental abnormalities and the location of the placenta, spot abnormal bleeding, ectopic pregnancies and many subtle birth defects. Here we present three rare syndromes diagnosed by 3D/4D sonography prenatally while screening a total of 3000 high risk pregnant women for the presence of congenital anomalies.

Case 1: Meckel Gruber Syndrome (Omim Entry - #249000)

A routine antenatal sonogram was performed on a 28 year old female presented with $G_3P_2L_2D_0A_0$ at 7th month amenorrhea, born to normal parents. The ultrasonogram revealed abnormal morphological features such as echogenic kidneys, occipital encephalocele, club foot, polydactyly (hands and foot) and median cleft lip palate suggestive of Meckel Gruber syndrome (MGS) (Figure 1). It's a rare lethal disorder, that affects all races and ethnic groups with equal incidence in both sexes and is inherited as an autosomal recessive disorder with an incidence is 1 in 13,250 to 1,40,000 live births worldwide [1]. It is often characterized by occipital encephalocele, polydactyly and bilateral dysplastic cystic (enlarged echogenic) kidneys that may result in oligohydramnious or anhydramnious [2]. The locus for MGS is mapped onto chromosome 17q21-q24 and exhibits some degree of locus heterogeneity [3]. Any mutations or variations in the genes located at this locus cause MGS. The list of candidate genes associated with the studied syndromes is presented in Table 1 while the pedigree of the proband with MGS is given in Figure 2. The proband was advised to undergo Fluorescence *In Situ* Hybridization (FISH) for trisomies (13, 18 and 21) (Figure 3) and was normal. The parents were counseled regarding the possibilities of several neurological abnormalities, their consequences on the outcome of pregnancy and were advised to take a decision regarding termination.

Case 2: Holt-Oram Syndrome (Omim Entry - #142900)

A 24 year old woman presented with $G_2P_1L_1D_0A_0$ at 28 weeks of gestation was referred to our institute for antenatal sonogram that showed features of skeletal dysplasia, hands and feet with only 4 digits, single umbilical artery, narrow LV outflow tract, echogenic focus in LV of heart and dilated loop of bowel, the symptoms suggestive of Holt Oram Syndrome (Figures 4 and 5).

It's an autosomal dominant disorder characterized by distinctive malformation of bones of the upper limbs and abnormalities of congenital cardiac and upper-limb malformations frequently occurs and are classified as heart-hand syndromes with the prevalence being 1 in 10,000 births. The females are most commonly affected

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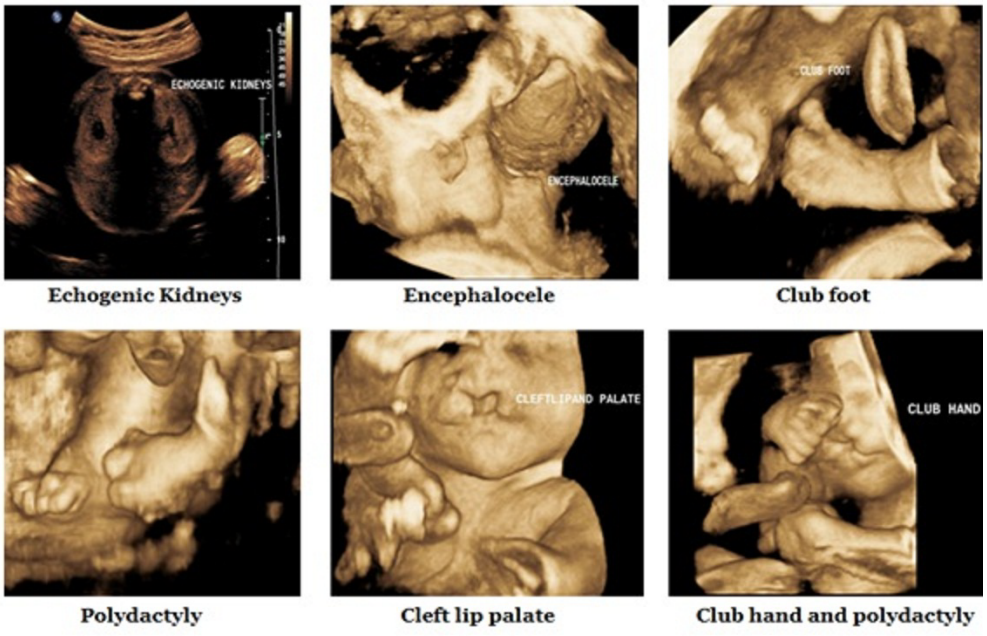

Figure 1: Ultrasonogram of fetus with Meckel Gruber syndrome.

Type of Syndrome	Gene	Function
Meckel Gruber	RPS6KB1 (17q23.1) Ribosomal protein S6 kinase	Growth and muscle building [10]
	SCN4A (17q23.3) Voltage gated Sodium Channel subunit alpha Nav1.4	Contraction and relaxation of muscles [11]
	CBX1 (17q21.32) Chromobox homolog	Mediates gene silencing [12]
	COL1A1 (17q21.33) Collagen type I alpha 1	Provides strength and supports many tissues that include cartilage, bone, tendon, skin, sclera, etc. [13]
	GFAP(17q21) Glial Fibrillary acidic protein	Cell-cell communication in central nervous system [14]
	MAPT (17q21.1) Microtubule associated protein tau	Regulates alternative splicing in nervous system [15]
	NOG (17q22) Noggin protein	Development of nerve tissue, muscles and bones [16]
	RARA (17q21) Retinoic acid receptor alpha	Leukemia [17]
	GALK1 (17q24)	Chemical signaling, building cellular structures, transporting molecules and producing energy [18]
Holt Oram	TBX5 (12q24.21) T-Box 5 protein	Formation of tissues and organs during embryonic development [19,20]
	RBM19 (12q24.21) RNA binding motif protein 19	Regulates ribosome biogenesis [21]
	TBX3 (12q24.21) T-Box 3 protein	Regulation of developmental processes [22]
Emanuel	T (11; 22)	-

Table 1: List of putative candidate genes implicated in MGS, HOS and Emanuel syndrome.

irrespective of race and ethnic backgrounds [4,5]. The HOS locus is mapped onto chromosome 12q24.21 that carries essential gene/s implicated and its products in the formation of tissues and organs during embryonic development. Any mutations at this locus may lead to variable expression of both cardiac and skeletal defects that have been considered as the chromosomal etiology of this disorder. The phenotypic effects of deletions depend mainly on the size and location of the deleted sequences on the genome that in turn can affect gene dosage (haploinsufficiency) and thus the resulting phenotype [6]. The couple was counseled about the condition and they opted for termination of pregnancy.

Case 3: Emanuel Syndrome (Omim Entry - #609029)

A 26 year old woman married to her first cousin, developed a bad obstetric history after the birth of her first child. Her second pregnancy was a pre-term (34 weeks) male child, who died after 3 days of birth. The third and fourth pregnancies resulted in abnormality of rectum and imperforate anus in the new born. She was referred to our unit at

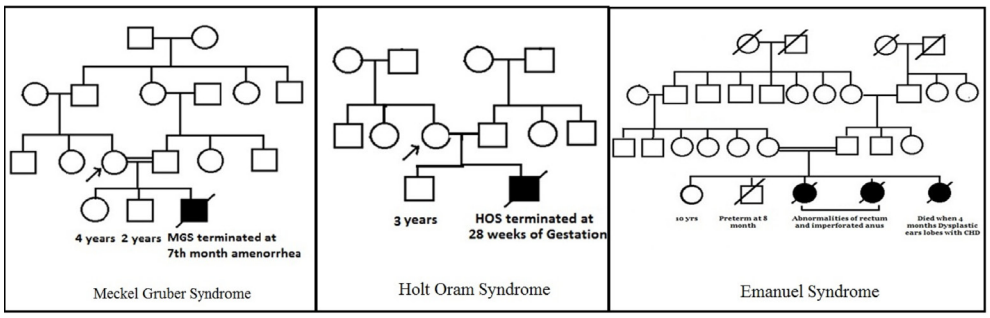

Figure 2: Pedigree of the proband with a fetus with Meckel Gruber syndrome, Holt Oram syndrome and Emanuel syndrome.

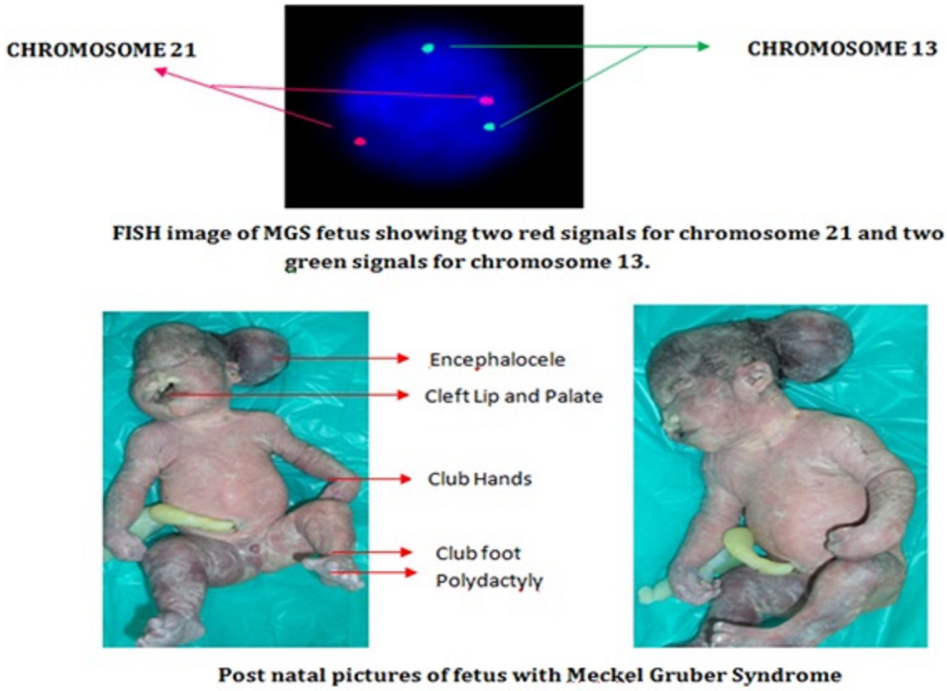

Figure 3: FISH image and post natal picture of fetus with Meckel Gruber syndrome.

6th month amenorrhea for prenatal diagnosis and counseling (Figure 5). Sonogram revealed a single live fetus of 17-18 weeks with intra-uterine growth retardation, dysplastic ears and congenital heart defects with small VSD along with moderate PDA and PDH confirmed by 2D ECHO were suggestive of Emanuel Syndrome; a rare disorder, first described by a cytogeneticist Dr. Emanuel. It has a distinct phenotype characterized by intrauterine growth restriction, facial dysmorphism, microcephaly, congenital cardiac defects and renal anomalies. Other common birth defects are malformations of anus referred as imperforate anus, where the opening to the anus is missing or blocked and intestinal defect called as diaphragmatic hernia where there is a defect in the muscular wall that separates the lungs and heart from the abdomen or a dimple in the skin just above the buttocks (sacral dimple). This chromosome imbalance consists of either a derivative chromosome 22 [der(22)] as a supernumerary chromosome with the following karyotype: 47,XX,+der (22) t (11;22) (q23;q11) in females or 47,XY,+der (22) t (11;22) (q23;q11) in males rarely [7]. Few cases may even show trisomy of chromosome 22 being inherited from one of the parents, most often the mother. The prevalence of this syndrome is not known, however, literature reports only about 100 cases [8,9]. FISH was performed and showed normal signals for Trisomy 13, 18 and 21 chromosomes (Figure 3) and was normal. The couple was counseled regarding the consequences on the outcome of pregnancy and was advised to take a decision regarding termination. However she continued her pregnancy and delivered a female child with a birth weight of 2.4 Kg associated with the mentioned deformities along with imperforate anus, moderate to large PDA with small mid muscular VSD and ASD. A small dimple was obvious at the lumbo sacral region of spine but meninges were not seen (Figure 4). The child developed acute bilirubin encephalopathy, pneumonia with septic shock and expired at 5 months of age (Table 1).

Conclusion

The importance of 3D/4D ultra which helps in the diagnosis of the rare disorder is indicated priority towards risk for high morbidity and mortality. Routine ultrasound scan done during pregnancy may

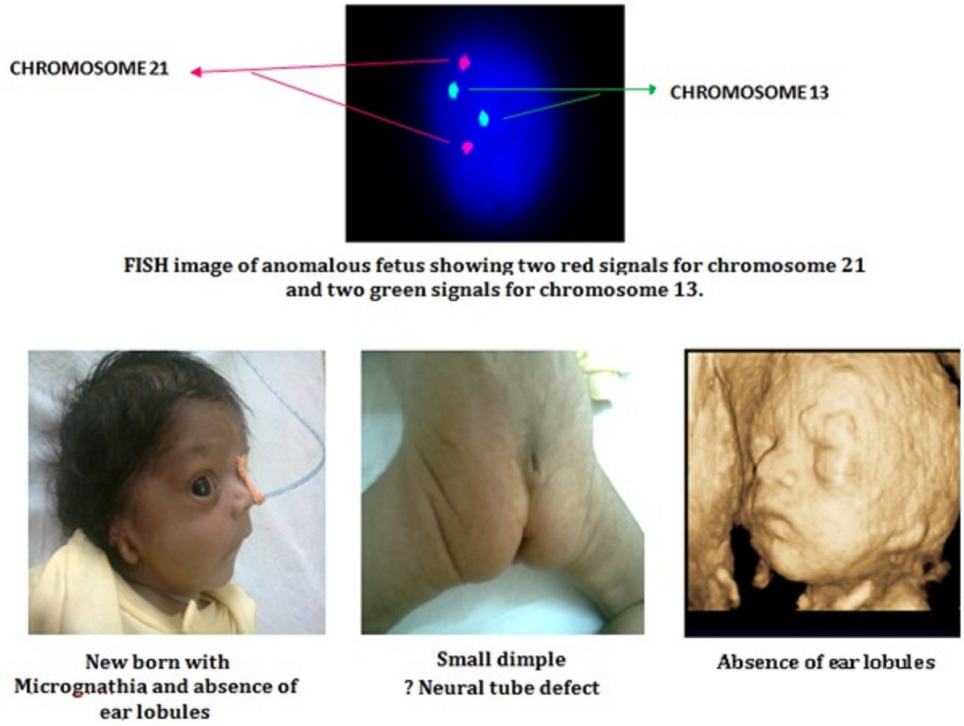

Figure 4: Ultrasonogram of fetus showing symptoms of Holt Oram syndrome.

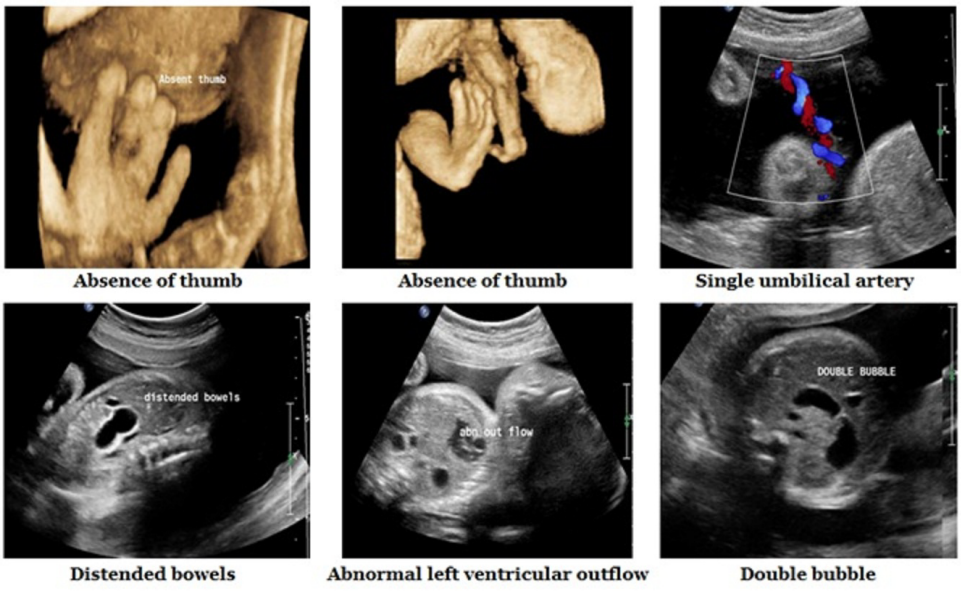

Figure 5: FISH image along with pre-natal and post-natal images of child with Emanuel syndrome.

pick up heart defect or any major birth defect if present but the 3D/4D ultrasound often assist in the study of many anatomical regions like face, extremities, genitalia etc. The prenatal diagnosis of the rare cases mentioned above followed by counselling will help the couple to understand the recurrent risk of syndromes in subsequent pregnancies and help to choose appropriate reproductive options.

Conflict of Interest

None.

Acknowledgement

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10. RPS6KB1: Ribosomal protein S6 kinase beta-1.

11. SCN4A: Sodium channel protein type 4 subunit alpha.

12. CBX1: Chromobox protein homolog 1.

13. COL1A1: Collagen alpha-1(I) chain.

14. GFAP: Glial fibrillary acidic protein.

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21. RBM19: Probable RNA-binding protein 19.

22. TBX3: T-box transcription factor TBX3.