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CASE STUDY

HOLT- ORAM SYNDROME - A CASE REPORT

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ABSTRACT

Holt-Oram syndrome (HOS) is characterized by mild-to-severe congenital cardiac defects and skeletal abnormalities of the upper limbs. The most common cardiac disorder is an ostium secundum atrial septal defect (ASD), followed by ventricular septal defect (VSD) and ostiumprimum ASD. Electrocardio graphlcal abnormalities such as various degrees of atrioventricular block have also been reported. In addition hypoplastic peripheral vessels of the upper limbs have been observed. One out of 100,000 live births is affected. More than 300 cases have been published, revealing a wide spectrum of clinical signs. HOS is an autosomal dominant disorder with complete penetrance. The underlying genetic defect was found on the long arm of chromosome 12 (12q2). Mutations in the TBX3 and TBX5 genes lead to a wide range of phenotypes. This condition can also occur due to denovo mutation. Detailed antenatal ultrasound examination and visualisation of all limbs& searching for fetalcardiac lesions is necessary for an antenatal diagnosis. If diagnosed early, MTP can be offered to selected cases. This case is reported to impress the need for early diagnosis and management.

INTRODUCTION

A 28 year-old, resident of Chidambaram, $G_3P_1L_1A_1$ with 9 months amenorrhea and with history of previous LSCS got admitted with one previous USG done at 20 wks gestation which did not show any anomalies. There was non-specific family history, non-consanguineous marriage, no exposure to teratogens. Routine history taking and examination were done. Her antenatal Ultrasound examination at 38 wks showed the following findings:

1. Radial bone was abnormal on right side and absent on left side.
2. Absent Thumb in both Upper limbs
3. Abnormal Position of Both Upper Limbs
4. Ventricular Septal Defect
5. Tricuspid atresia

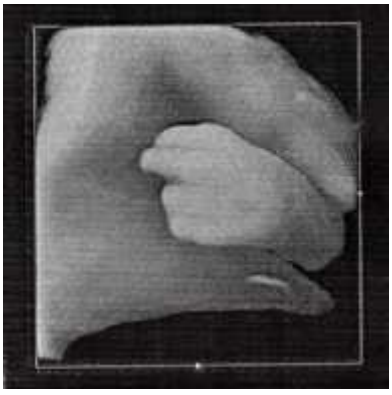

Fig. 1 Ultrasoundpicture showing Absent Thumb in left Hand

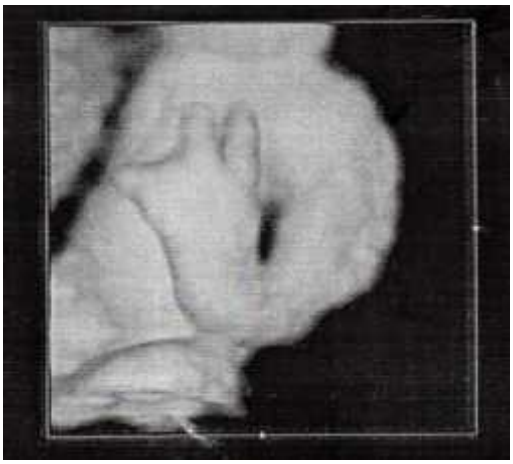

Fig.2 Ultrasoundpicture showing Absent Thumb in right Hand

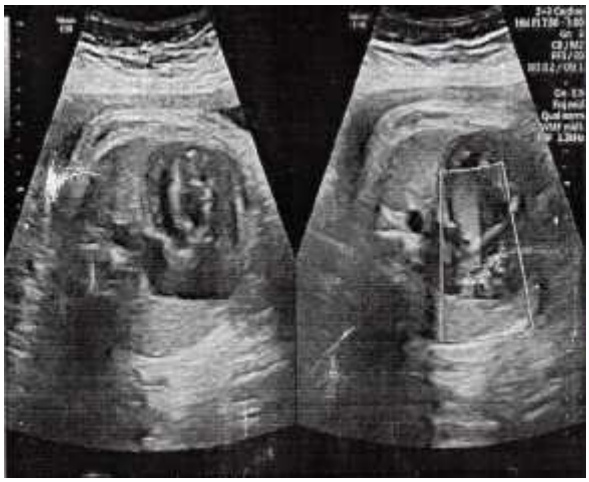

Fig.3 Ultrasound picture showing fetal Heart

Fig.4 Baby after delivery

Patient underwent emergency LSCS at 38 weeks of gestation and delivered a live male of birth weight 2.4 kg. APGAR was poor and baby died inspite of resuscitation. Baby had abnormal position of left forearm and absent thumb on both sides. X-ray findings confirmed absent radius on left side. Karyotyping was not performed due to financial constraint. Parents did not agree for autopsy of the baby.

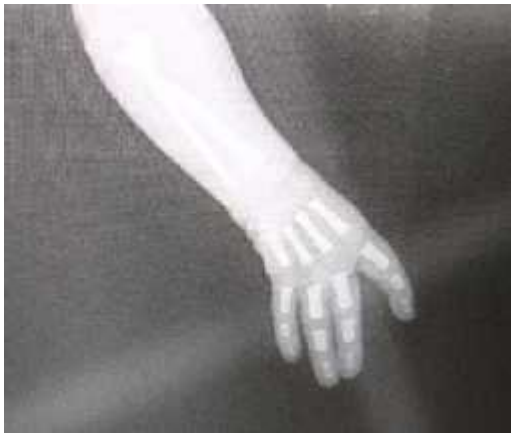

Fig. 5 X-ray showing abnormal radius bone and Absent Thumb in Right Hand

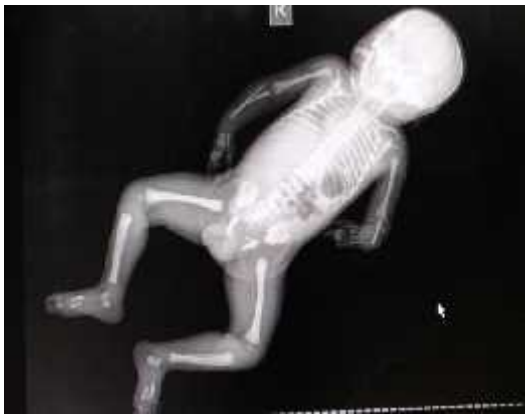

Fig.6 Abnormal radius bone found in the patient

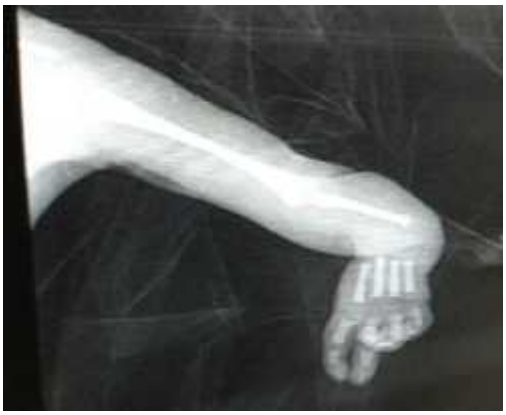

Fig.7 Absent Radius and absent Thumb in Left Side

What is Halt-Oram Syndrome?

Holt-Oram syndrome is an autosomal-dominant condition characterized by congenital cardiac and forelimb anomalies.[1] It was first reported in1960 by Mary Clayton Holt and Samuel Oram.[2] They found an atrial septal defect and a congenital anomaly of thumbs in members of 4 generations in a family. They described as a triad of ASD, Conduction disturbances, and hand Anomalies. Various Studies found that mutations of

the TBX3 and TBX5 gene, a member of the T-box family that found on the long arm of chromosome 12 (12q2).[3] These genes play an important role in cardiac and skeletal development. Mutations in these two T-box genes lead to defect in congenital heart defect and limb abnormalities[4,5]. Mutations in the TBX3 and TBX5 genes lead to a wide range of phenotypes. Sporadic cases can also occur due to denovo mutation.

Clinical features

More than 300 case report has been published with various clinical features of Holt-Oram Syndrome.[6] The Incidence of HOS is one out of 100,000 live births,[2] and it occurs with wide ethnic and geographic distribution. All patients with HOS have upper limb anomaly and about 85% to 95% have cardiac malformation.[7,8] Thus, the criteria for diagnosis include either the presence of cardiac malformations, conduction defects and radial ray abnormalities (or both) in an individual, or the presence of radial ray abnormalities with or without cardiac malformations or conduction defects in individuals with a family history of HOS.[9] The family history should be consistent with autosomal-dominant inheritance.

Upper Limb anomalies

Skeletal abnormalities affect the upper limbs exclusively; lower limb abnormalities have not been reported.[1] The abnormalities are always bilateral and often asymmetric, predominantly involving the radial ray. Amputation of rudimentary or hypoplastic fingers was reported. The thumb is the most commonly affected structure and can be triphalangeal, hypoplastic, or completely absent. Abnormalities range from minor (clinodactyly of the fingers, limited supination of the forearms, and sloping shoulders) to severe (reduction deformities, including phocomelia and ectromelia).[1] Poznanski *et al.*[10] demonstrated that carpal abnormalities are more specific for HOS than changes in the thumb. Other radiographic abnormalities include posteriorly and laterally protuberant medial epicondyles of the humerus, hypoplastic clavicles, shortened radii, ulnar hypoplasia (occurring only in patients with radial defects), scoliosis, abnormal ribs and scapular anomaly.

Cardiac defects

Secundum-type of atrial septal defect (ASD) and ventricular septal defect (VSD) are the most common heart defects. Other cardiac defects range from asymptomatic conduction disturbances (first-degree heart block) to multiple structural defects. Almost every type of cardiac anomaly has been reported, either singly or as part of a group of multiple defects.[11-13] Sudden death from heart block has been reported. Bruneau *et al.*[14] summarize the defects in 240 patients. Among these patients, 58% had ASD, and 28% have VSD. Less common anomalies, such as conduction defect, Truncus Arteriosus, mitral valve defect, patent ductusarteriosus, and tetralogy of Fallot, occur in 18%, 8%, 4%, 4%, and 3%, respectively.

In an earlier series of studies, heart defects in 189 patients were classified by severity.[8] Among these patients, 66% had single abnormalities, including isolated conduction defects; 16% had "mild" combinations consisting of two or three malformations (eg, ASD, VSD); 11% had "moderate" combinations that required more complicated surgical repair (eg, tetralogy of Fallot and endocardial cushion defect); and 6% had "severe" combinations with life-threatening defects, including hypoplastic left heart, total anomalous pulmonary venous return, and truncusarteriosus.

Diagnosis

Diagnosis of heart defects requires electrocardiography and two-dimensional echocardiography with Doppler.[1] Cardiac catheterization may be required to fully define a defect. Clinical recognition of subtle limb anomalies in patients with HOS can require both physical examination and radiographs of the upper extremities.[1]

Differential Diagnosis

The following autosomal-dominant conditions need to be considered for differential diagnosis:[1] Fanconi anemia syndrome, Thrombocytopenia-absent radius, Heart-hand syndrome II, Heart-hand syndrome III, Okihiro syndrome, Long thumb brachydactyly syndrome, VACTERL association, etc.

DISCUSSION

Detailed antenatal ultrasound examination is needed to diagnose the limb anomalies. Genetic counselling should be provided to all patients with family history of HOS. Of pro-bands, 60% to 70% have an affected parent, and 30% to 40% have a de novo mutation. Evaluation of both parents is recommended, including physical examination and radiographs of the upper extremities to detect subtle changes of the thumb and carpal bones. Examination of the heart, including electrocardiogram and echocardiogram are recommended.[1]

Risk to siblings depends on the genetic status of the parents. If one of the parents is affected, the siblings of a proband have a 50% risk of inheriting the disease-causing mutation. When the parents are clinically unaffected, the risk to the siblings of a proband appears to be low. Each individual with HOS has a 50% chance of inheriting the disease-causing mutation.[1] Operative treatment may be needed for congenital heart defects. Prognosis is poor even after surgical correction of cardiac lesions.[15-17]

CONCLUSION

This case reporting is done to stress the importance of antenatal screening by ultrasound examination for congenital anomalies. Visualisation and measurement of all long bones is a simple procedure which would have diagnosed the condition in early pregnancy. Proper ultrasound reporting would have avoided the psychological trauma the patient had to undergo and she would not have had to go upto term gestation and undergo a surgical procedure for delivery of a baby with anomalies which has poor chances of survival.

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