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Case Study

A CASE OF HOLT ORAM SYNDROME WITH DEXTROCARDIA

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Abstract

Holt-Oram syndrome (HOS) is an autosomal-dominant condition characterized by congenital cardiac and forelimb anomalies. It is caused by mutations of the TBX5 gene, a member of the T-box family that encodes a transcription factor. Secundum-type 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 .The cause of these disparate clinical features is unknown. Here we report a case of a new born baby with absent left thumb and radius and the presence of an ostium secundum atrial septal defect suggestive of holt oram syndrome along with an incidental finding of asymptomatic dextrocardia..The purpose of the report is to highlight the varied clinical presentations of this rare entity.

Keywords- Holt Oram syndrome, TBX5 gene, autosomal dominant, limb defects, ostium secundum ASD

Introduction

Holt and Oram first described this syndrome in 1960 [1] when they reported on a family with atrial septal defects and congenital anomalies of the thumbs. The prevalence of HOS is 1 in 100,000 live births, and it occurs with wide ethnic and geographic distribution. Its clinical manifestations have proved to be variable, but with complete penetrance. All patients with HOS have upper limb anomaly and about 85% to 95% have cardiac malformation. Strict diagnostic criteria for HOS comprise the presence of preaxial radial ray malformation of at least one upper limb along with a personal or a family history of septation defects and/or atrio ventricular conduction disease[2]. If this criterion is met

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TBX5 mutations are bound to be found in 74% of cases.

The present case report intends to highlight the possibility of dextrocardia in a case of holt oram syndrome thereby enabling clinicians to be more vigilant during the follow up of such syndromes in future. It also aims at providing an opportunity for practitioners to take prompt measures in a timely manner with respect to genetic counselling and newer diagnostic modalities like gene sequencing in developed nations with no financial constraints for such interventions.

Case Report

A full term newborn male, the product of a non-consanguineous marriage with uneventful normal pregnancy, delivered to a 25-year old primigravida Indian mother was brought to the Newborn Care Unit, 4 hours after the birth. The mother complained of feeding difficulty in the neonate but was much more perplexed when she narrated about the absence of the left thumb and a deformity of the left wrist which came into her notice while attempting to feed the child.

The mother was not known to have any medical illnesses, radiation or drug exposure during the antenatal period. There was no family history of congenital or cardiovascular anomaly [Fig 1.]. She had regular antenatal checkups from a local hospital but abdominal ultrasounds were not done due to lack of facilities. The baby was born via vaginal route, cried immediately after birth and had good apgar scores-9/10 at 5 minutes and 10/10 at 10 minutes.

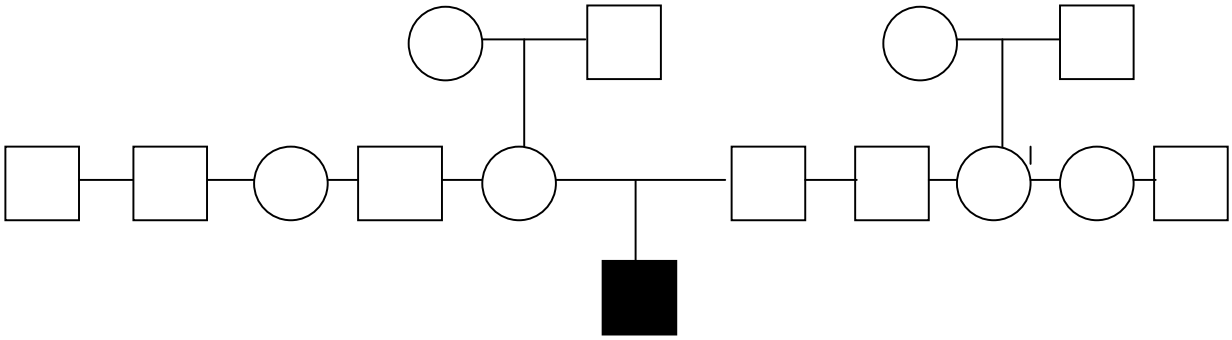

Fig 1 .Pedigree chart of the family of the patient.

Initial physical examination revealed an alert and active pink baby with good cry and reflexes (Moro-complete, good suck) with a CRT<3 sec and stable vitals. There was no evidence of jaundice, bleeding, breathing difficulties, abnormal movements or postures, and the anterior fontanelle was not bulging. Anthropometric measurements revealed normal parameters (Weight-2.53kg,Length-47cm,Head circumference-35cm).However the left thumb and the left radius was absent and there was an abnormal radial deviation of the left hand(Fig.2)

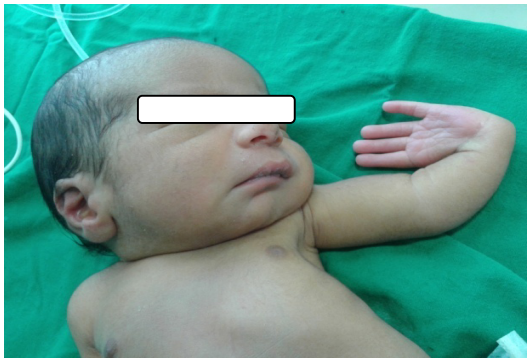

Fig 2.Absent left thumb and radial deviation of left hand.

No other gross morphological anomalies could be detected but detailed examination revealed increased intensity of heart sounds on the right side with no appreciable murmurs.

The child was investigated in detail- Complete blood count: normal (no thrombocytopenia), Random blood sugar-68mg/dl, Renal function tests-normal. Chest X-ray revealed dextrocardia with the remaining lung fields being normal(Fig.3).

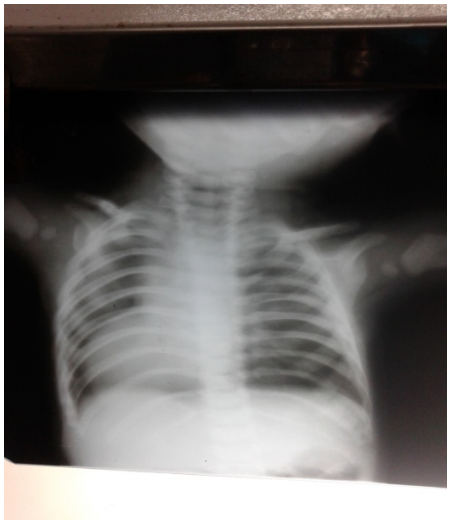

Fig.3 Chest Xray showing dextrocardia.

Skeletal survey was done and an antero-posterior view of the left forearm and wrist revealed absent thumb, radius and carpal bones (Fig.4).Electrocardiography revealed dextrocardia with inverted P waves in lead 1 but no conduction abnormalities. Abdominal ultrasonography turned out normal and finally a 2D echocardiography was done which revealed an ostium secundum type atrial septal defect measuring 3.9mm,dextrocardia and normal ventricular dimensions and function. Genetic study for TBX5 gene could not be done due to limited resources.

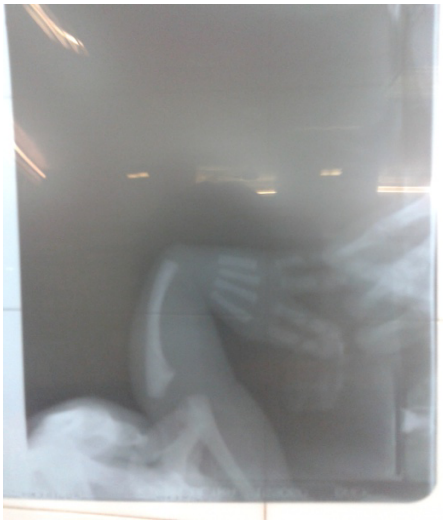

Fig.4 Xray Left forearm and wrist AP view revealing absent thumb, radius and carpal bones

The baby is at present 45 days old, thriving well and asymptomatic with regard to his cardiac lesion. Surgical corrections of the limb and cardiac defects are future plans as the child grows older and would be regularly followed up in the paediatric, orthopaedic and cardiology clinics.

Discussion

Holt Oram Syndrome (*HOS, atrio digital dysplasia, heart hand syndrome)* is a rare developmental disorder characterised by cardiac anomalies and distinctive malformations of the bones of the upper limb. Described first in 1960 by Holt and Oram , the syndrome is inherited as autosomal dominant with near complete penetrance and variable expression.

The gene responsible has been mapped to band 12q24.1 which encodes the human transcription factor TBX5. TBX5 acts synergistically with NKX2-5 and promotes cardiomyocyte differentiation by binding to the promoter of the gene encoding cardiac-specific natriuretic peptide precursor type A (NPPA).Mutations in this gene produces abnormal expression of the cardiac and limb specific T-box transcription factors that lead to the malformations described in HOS. The T-box gene family is a group of related genes that play a critical role in the human embryonic development[3]. Approximately 40% of cases represent new mutations.

The cardinal manifestations of HOS are dysplasia of the upper limbs and cardiac anomalies. The skeletal deformities range from mild to severe including triphalangeal thumbs, short ulna or humerus, carpal bone dysmorphism, thumb or radial aplasia (as in our case)and even phocomelia[4]. Although bilateral the left side often has a more significant affection. It results from injury to the developing arm during fourth to seventh week of pregnancy. In some cases this can be caused by exposure to factors in the environment including compression, inflammation, nutritional deficiency and chemical and drug exposure.

Congenital heart defect is the most important cause of morbidity and mortality in these patients, secundum ASD being the most common lesion. Others include ventricular septal defect(VSD), atrio-ventricular block, mitral valve prolapse and pulmonary stenosis. Bruneau *et al.* summarizes the defects in 240 patients[5]. Among these patients, 58% had ASD, and 28% have VSD. Approximately 20% of patients have more complex cardiac malformations such as tetralogy of fallot, truncus arteriosus, cardiac arrhythmias, endocardial cushion defect and hypoplastic left heart.

Dextrocardia per se as in our case is a rare association though asymptomatic at presentation. The following autosomal-dominant conditions were considered for differential diagnosis before the final diagnosis of HOS was made in our case:

• **Fanconi Anaemia**: Characterized by congenital malformations of the thumbs, forearms and hand, skin pigmentation, progressive bone marrow failure with pancytopenia, typically in the first decade; and increased risk for myelodysplasia or acute myelogenous leukemia. Presence of secundum ASD in our case almost rules out the possibility of this entity.

•**Thrombocytopenia Absent Radii(Tar Syndrome)**: Both radii are always absent; the thumbs are always present. On the contrary, radial aplasia in HOS is invariably associated with hypoplasia or absence of the thumb .

•**Vacterl Association-** Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, and Limb anomalies association: Radial defects are usually unilateral and accompanied by characteristic other malformations such as imperforate anus, trachea esophageal fistula. The presence of radial defect without other multisystem anomalies rules out this entity.

• **Okhiro Syndrome:** A combination of Duane syndrome (a congenital eye-movement disorder resulting from abnormal development of cranial nerve VI and characterized by absence of abduction of the globe and narrowing of the palpebral fissure on adduction of the globe), upper extremity reduction defects, and cardiac malformation].

The present case seems to be sporadic since the parents were apparently healthy. However evaluation of both parents is

recommended, including physical examination, skeletal survey of the upper extremities, electrocardiography and echocardiography to detect subtle changes of the upper limb bones and the heart.

Genetic counselling should be provided to all patients with HOS. Of pro-bands, 60% to 70% have an affected parent, and 30% to 40% have a *de novo* mutation. Risk to siblings depends on the genetic status of the parents. If one of the parents is affected, the siblings of a pro-band have a 50% risk of inheriting the disease causing mutation. When the parents are clinically unaffected, the risk to the siblings of a pro-band appears to be low.

Molecular genetic testing of *TBX5* is currently available only on a research basis. Using gene sequencing of the*TBX5* coding regions or mutation scanning (single-strand conformation polymorphism [SSCP] followed by sequencing of exons with abnormal band patterns), the mutations can be detected which is not possible in a developing country like ours as in the present scenario. Nevertheless, we can hope for the same in future and the syndrome after diagnosis clinically, by skeletal survey, ECG and echocardiography can be considered for surgical interventions to correct the limb and cardiac anomalies, pertaining to follow up for years.

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