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Atypical Presentation of Holt-Oram syndrome: A Case Report

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Abstract

Holt-Oram syndrome (HOS) is an autosomal dominant disorder, a mutation in TBX5 gene located on chromosome 12 (12q24.1) involving the upper limb and the heart, causing malformations like atrial septal defect. Herein, we report a rare case of HOS with atrial septal defect and ventricular septal defect with severe pulmonary arterial hypertension in a three-year-old child.

***Key Words*:** Child, Heart-hand syndrome, Holt-Oram syndrome, ventricular septal defect.

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1- INTRODUCTION

HOS is a rare congenital disease, which affects the upper limbs and heart with an incidence of approximately 1 in 1, 00,000 live births. It is a hereditary disorder with autosomal dominant nature and has complete penetrance. It is linked to a single gene TBX5 "protein-producing" mutation with gene map locus 12q24 and is the most commonly occurring heart–hand syndrome (1-3). Congenital cardiac and upper-limb malformations frequently occur together and are classified as heart-hand syndromes. The common limb abnormalities are preaxial radial ray abnormalities such as radial agenesis and radial aplasia, whereas the most common cardiac defects include atrial septal defect. Rare but other cardiac associations include pulmonary stenosis, mitral valve prolapse, and arrhythmias in the form of atrioventricular blocks. More complex cardiac lesions such as tetralogy of Fallot, endocardial cushion defects, and total anomalous pulmonary venous return are also noted (2-4). Herein, we report a rare case of HOS with ventricular septal defect (VSD), and atrial septal defect (ASD) with severe pulmonary arterial hypertension.

2- CASE PRESENTATION

A 3-year- old male child born out of a third degree consanguineous marriage was brought with complaints of abnormal development of limbs since birth and cough and cold since 4 days in the month of March at AVBRH Sawangi, Wardha, Maharashtra, India. Patient had history of recurrent cough and cold from infancy period. He was born full term, appropriate for gestational age via normal vaginal delivery. He had two elder siblings who are normal. There was no family history of heart diseases or limb anomaly. On general examination, the child was pale with no cyanosis and clubbing. He had bilateral agenesis of first finger and absent thenar prominence. His Right arm was shortened with three digits. There were four digits in his left hand. Pronation and supination was absent on the right side and was limited on the left side with restricted movements in the wrist. Upper limb was shortened with only 4 digits in the left hand and 3 digits in the right hand (**Figure.1**).

No chest deformity. Harrison sulcus was present. Vision and Hearing assessment was normal. Lower limbs and Spine were normal. He was a developmentally normal child with a height of 87.5cm, weight of 9.2kg and head circumference: 47cm. He has acute on chronic malnutrition. His HR-110/min, BP (left arm)-96/60mmhg, SpO2 in right arm: 97% and right leg-98%. Cardiovascular examination revealed a Short systolic murmur with fixed split second heart sound with loud P2 in left 2nd intercostal space (**Table.1**). On Abdominal examination, there was no hepatosplenomegaly. Air entry was bilaterally equal on respiratory system examination. CNS examination revealed no focal neurological deficits.

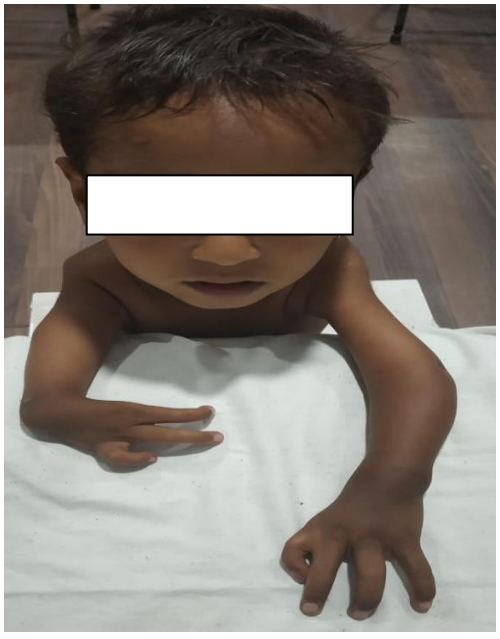

Fig.1: Upper limb shortening with less number of digits. Right limb shorter than the left.

Investigation	Findings
1. Complete blood count	
Haemoglobin	10.6gm/dl
Total leucocyte count	14,900 cells per cu mm.
Platelet count	4, 08,000 platelets per microlitre.
2. Right upper limb X-ray	Absence of proximal humerus and distal radius with two carpal bones and three metacarpals visualised. Absence of right thumb. Distal epiphyseal centre of ulna and proximal epiphyseal centre of humerus was not visualised which indicates lack of bone maturity according to the age of the patient (**Figure.2**).
3. Left upper limb	Absence of radius with three metacarpals. No carpal bones seen. Thumb and fourth finger are absent. Epiphyseal centre of ulna is not visualised (**Figure.3**).
4. Chest X-ray	Cardiomegaly with pulmonary plethora.
5. ECG	Biventricular hypertrophy with left axis deviation.
6. 2D echo	Modarate ostium secundum type of atrial septal defect with moderate size perimembranous type of ventricular septal defect with pulmonary arterial hypertension.

ECG*:* Electrocardiogram, 2D echo*:* 2D Echocardiography.

3- DISCUSSION

Holt-Oram syndrome (HOS) is an autosomal dominant disorder characterized by congenital malformation of the upper limbs and the heart. A heterozygous mutation in the TBX5 gene on chromosome 12q24.1 causes HOS. This gene is responsible for encoding a transcription factor, which regulates the expression of other genes in the development of the heart and the limbs. Holt and Oram first described this syndrome in 1960. Clinical manifestations are variable, but upper limb abnormalities are always present. The cardinal manifestations of HOS are dysplasia of upper limb that ranges from minor findings including hypoplasia of thumb, clinodactyly, brachydactyly, triphalangeal thumbs, carpal bone dysmorphism, shortness of ulna, shortness of humerus, aplasia of radius to phocomelia and cardiac abnormalities. Carpal bone abnormalities are the only findings present in every affected individual, although these anomalies may be evident only radiographically in some patients. Other radiographic abnormalities include posteriorly and laterally protuberant medial epicondyles of the humerus, hypoplastic clavicles, shortened radii, and ulnar hypoplasia. Skeletal deformities cover upper extremities only, and these abnormalities may be unilateral or bilateral and symmetric or asymmetric. Most cases are unilateral and affect the left side (3-5).But in our case we found bilateral involvement of the upper limb with right

side more involved than the left side. It can be detected intrauterine during the anomaly scan presenting as abnormal upper limb development. It is usually detected after birth (6). The congenital heart malformations most commonly observed are ostium secundum type of Atrial Septal Defect (ASD). The septal defects may be mild or can be more severe, which can further lead to problems such as pulmonary hypertension, congestive heart failure, or infective endocarditis. Although baby may present at birth with sinus bradycardia and first-degree atrioventricular (AV) block, AV block can progress unpredictably to a higher grade including complete heart block with and without atrial fibrillation (6-8).

A number of other disorders may present as having cardiac defects and skeletal deformities similar to Holt–Oram syndrome such as thrombocytopenia absent radius syndrome (TAR syndrome), Roberts syndrome, thalidomide embryopathy, and fanconi anemia. TAR syndrome is diagnosed in patients with absent radii in bilateral upper limb though thumbs are present, along with thrombocytopenia. It is associated with skeletal abnormalities, heart and genitourinary abnormalities (9). Duane-radial ray syndrome is an autosomal dominant disorder characterized by upper limb anomalies, ocular anomalies and renal anomalies hence was previously called as acro-renal-ocular syndrome.

It can also be associated with sensorineural deafness and gastrointestinal anomalies, such as imperforate anus. The Holt-Oram syndrome (142900), caused by mutation in the TBX5 gene (601620) on chromosome 12q24, shows similar anomalies of the upper limb, but can be differentiated from Duane-radial ray syndrome by the absence of ocular and renal anomalies and the presence of severe congenital heart defects (10). In Holt–Oram syndrome, the radial aplasia is associated with thumb aplasia or hypoplasia without any hematological disturbance and with a positive family history of limb deformities (5-6). It does not affect the lower limbs because of the fact that mutant gene affects the embryogenesis during the 4th and 5th week of intrauterine life when the lower limbs are not differentiated. Both physical features and family history can help establish the diagnosis of HOS. Specifically, a family history of congenital heart malformations should warrant further investigation with an electrocardiogram and echocardiogram.

In addition, upper limb X-rays can demonstrate various abnormalities. The management of individuals with HOS optimally involves a multidisciplinary team approach, with specialists in medical genetics, cardiology, and orthopedics, including a specialist in hand surgery. Upper limb abnormalities may require corrective or reconstructive surgery in addition to physical and occupational therapy. Those with cardiac malformations may require medications or surgical correction. Current evidence shows that prognosis depends on the severity of the cardiac manifestations; patients with severe morphological electrical cardiac manifestations have worse prognosis and may need surgery (7, 8, 11, 12).

4- CONCLUSION

In conclusion, we report a rare case of Holt-Oram syndrome with an upper extremity deformity (right side involved more than the left side) with moderate size ostium secundum type of atrial septal defect and moderate size perimembranous type of ventricular septal defect with severe pulmonary arterial hypertension. Therefore it is essential to evaluate for cardiac defects in any child presenting with a congenital upper limb deformity.

5- ABBREVIATIONS

HR: Heart rate.

BP: Blood pressure.

SpO2: Oxygen saturation.

P2: Pulmonary S2.

CNS: central nervous system

6- CONFLICT OF INTEREST: None.

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