A Case Report on Holt Oram Syndrome
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ABSTRACT
Holt Oram Syndrome (HOS) falls in rare prevalence category with probability of 0.7 in 100,000 live births. It is a rare autosomal dominant multiple malformation syndrome characterized by abnormalities affecting hands, wrists, arms, congenital heart defects and/or conduction problems. Genetic mutations observed in TBX5 gene is attributed as the main cause of HOS. Our patient in his late 40s was diagnosed with Holt Oram Syndrome. He presented with typical conditions of congenital heart abnormalities (ASD) and upper limb malformations.

Keywords: ASD, Congenital heart defects, Holt Oram syndrome, TBX5 Gene, VSD.

INTRODUCTION
Holt Oram Syndrome (HOS) also termed as Heart Hand Syndrome falls in the category of rare diseases involving skeletal abnormalities of upper limbs (Hands, Wrists & Arms), congenital heart malformation and cardiac conduction abnormalities. The cardiac defects involve shunts in heart chambers causing Atrial Septal Defect, Ventricular Septal Defect and Arrhythmias. Here we present a case report of South Asian male from Pakistan diagnosed with HOS in grown-up/adult age bracket to emphasize upon diagnostic considerations in the proband and the family, keeping in view the importance of early diagnosis.

CASE REPORT
A 48-year old man resident of Karachi, Pakistan reported to Cardiology Clinic, Pakistan Naval Ship Shifa Hospital Karachi with complaint of SOB on exertion for the last 20 days. Breathlessness was sudden in onset not associated with chest pain, syncope or palpitations. This used to be aggravated on exertion and led to moderate limitation of physical activity (NYHA Class-II), relieved on taking some rest and sitting upright with episodes of nocturnal breathlessness. He was a diagnosed case of epilepsy with a history of smoking. Physical examination revealed polydactyly with syndactyly of the thumb bilaterally (Figure-1). No other limb abnormalities were observed.

His pulse was 95 beats/min (irregularly irregular), BP 140/90 mm of Hg, Temperature 98.6°F, SpO2 96% on room air and BSR of 132mg/dl. Cardiovascular examination revealed normal S1 and fixed wide splitting of second heart sound along with ejection systolic murmur of Grade-III/VI at upper left sternal border. Chest auscultation revealed bilateral basal crepitations. Rest of the examination was unremarkable. His ECG revealed Atrial Fibrillation with fast rate and right bundle branch block (Figure-2).

Chest X-Ray PA view revealed cardiomegaly mainly of right atrium and right ventricle with prominent lung markings (Figure-3).

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Plain radiographs of both hands revealed underdeveloped phalanges and syndactyly of thumb (Figure-4).

2D echo showed normal sized LV with severe systolic dysfunction atypical septal motion with severe global hypokinesia with ejection fraction of 25%, right ventricle was enlarged in size with mild dysfunction. There was Right Atrial enlargement with moderate to severe TR depicting moderate pulmonary arterial hypertension. Atrial Septal Defect (ASD) secundum type was noted with left to right shunt measuring in size 20 mm and dilated coronary sinus (Figure-5).

The patient was taken to cath lab with a view to calculate pulmonary/systemic shunt ratio (QP/QS) and pulmonary vascular resistance. During cardiac catheterization he developed frequent episodes of atrial fibrillation and haemodynamic instability due to which the procedure had to be abandoned for patient safety.

The patient was diagnosed with Holt Oram Syndrome clinically. However, the patient’s family history was unremarkable for any congenital malformations. Since his admission, the patient was managed on IV Heparin along with Tabs Loprin, Metoprolol, Digoxin, Captopril, Lasoride and Epival.

**DISCUSSION**

Holt Oram Syndrome was first diagnosed in 1960 by Mary Clayton Holt and Samuel Oram. It is also known as Heart Hand Syndrome. The disease falls in rare prevalence category with probability of 0.7:100,000 live births. It is a rare autosomal dominant multiple malformation syndrome which is characterized by abnormalities affecting hands, wrists, arms, congenital heart defects and/or conduction problems. Upper Limb malformations due to aplasia or hypoplasia may involve arms & wrists or abnormal growth of carpal and thenar bones. Cases of abnormal pronation and supination in forearm have also been seen including abnormal opposition of the thumb and sloping shoulders. The people suffering from HOS may have problem in extending fully or rotating their arms due to de-shaped or missing collar bones and shoulder blades. An abnormal carpal bone has presence in every affected individual and is the only probable evidence of disease.

About 75% of the patients of HOS are reported to have cardiac defects. These cardiac defects are Atrial Septal Defect or Ventricular Septal Defect of different size and location. Other heart defects including Patent Ductus Arteriosus (PDA) have also been observed beside pulmonary hypertension. Few patients with HOS have cardiac conduction disease which may result in Cardiac Bradycardia or right bundle branch block (RBBB) or Atrial Fibrillation. Health problems of cardiac conduction disease get worse with age progression.

HOS is caused by genetic mutations in the TBX5 gene which is located on long arm of chromosome no 12 (12q2). TBX5 is found particularly in the heart and forelimb, besides being in lungs and eyes. The gene belongs to T-box family containing around 180 amino acid residues. The amino acid sequencing of proteins
Holt Oram Syndrome

encodes transcription factors required essentially for development of organs and body parts. Mutations involved in HOS are mostly of the T-box domain. The TBX5 gene has its maximal effect across the heart tube inflow tract. Beside this it also has expressions of presence in sinus venosus, atria, atrioventricular canal, left ventricle (LV) and right ventricle trabeculae. Thus, it has serious effects on cardiac conduction system. TBX5 gene is also found to have effects in forelimb development and outgrowth as well. The inheritance risk of TBX5 gene pathogenic variant to an offspring is considered as 50%.

HOS is diagnosed primarily on clinical grounds. The criteria for HOS may include Congenital Heart Disease with or without conduction defects and abnormalities in minimum of one upper limb. Upper limb abnormalities are mostly investigated and identified through X-Ray examination and for Congenital Heart Disease Echocardiography is test of choice beside other radiographic investigations. Diagnosis of disease in individuals with mild symptoms is usually belated until they experience conduction dysfunction. The differential diagnosis primarily includes heart-hand syndrome Type-2 (Tabatznik syndrome), heart hand syndrome Type-3 (Spanish Syndrome), Slovenian type heart-hand syndrome, brachydactyly-long thumb, Schinzel Syndrome & SAL4-related disorders to include Duane radial ray and acro-renal-ocular syndrome. Treatment regimen for the disease revolves around symptomatic and supportive therapies.

CONCLUSION

HOS is a rare and fatal disorder which can be picked easily if clinicians have an insight about the morphological defects observed in upper limbs and congenital cardiac defects. The symptoms are prevalent since birth but are usually picked in adult hood with disease progression. This case report signifies that HOS should be considered in patients with upper limb malformations and congenital cardiac abnormalities as the diagnosis of our patient could not be established for over 4 decades. Being a genetic defect of TBX5 gene its early diagnosis may help in taking conscientious decisions by individual before planning a family.

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Author’s Contribution

Following authors have made substantial contributions to the manuscript as under:

ANK: Manuscript writing, concept and approval of the final version to be published
ESM: Intellectual contribution, concept and approval of the final version to be published
SOA: Proof reading, Intellectual contribution and formatting
AM: Drafting the manuscript, proof reading and critical review
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Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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