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Holt Oram Syndrome: Exploring the Heart Through Bones

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Abstract

Holt Oram Syndrome is an autosomal dominant disorder that is characterized by defects in carpal bones of the wrist, abnormalities of the thumb and cardiac anomalies like atrial or ventricular septal defects. It is caused due to a single-gene *tbx5* "protein-producing" Mutation with gene map locus 12q24. Hereby we report a case of 30-year-old lady of Holt Oram syndrome with morphological defects in both upper limbs and Ostium seccundum type of Atrial Septal defect.

Keywords: Holt Oram Syndrome, Atriodigital dysplasia, Atrial septal defect, *TBX5 gene*

INTRODUCTION

Holt Oram Syndrome is an autosomal dominant disorder that is characterized by defects in carpal bones of the wrist, abnormalities of the thumb and cardiac anomalies like atrial or ventricular septal defects. Hence, it is also known as atriodigital dysplasia. It was first described in 1960 by Mary Holt and Samuel Oram, in a four-generation family with atrial septal defect and thumb abnormalities. The estimated incidence is one in 100,000 live births. The culprit gene for this syndrome has been mapped to *TBX5* gene on chromosome 12q24.1.

Case Report

We present a case of a 30-year-old female with evidence of morphological defects of both upper limbs since birth with no prior evaluation with respect to the etiology.

She presented to the emergency department with symptoms of chest pain and palpitations for the past 5 days. She had history of recurrent episodes of cough and effort intolerance since childhood without any history of cyanotic spells.

Physical examination revealed a regular pulse with pulse rate of 65 beats per minute, BP of 100/70 mm hg, SpO_2 of 95% at room air, an elevated JVP, bilateral pedal edema with no signs of cyanosis and clubbing.

On musculoskeletal examination, Fingerisation of thumb in both hands along with fusion of carpal bones was noted (Figure 1). The radii and clavicles on both sides were normal.

Fig. 1: Fingerisation of thumbs

Cardiovascular examination revealed a left parasternal systolic heave, fixed splitting of the second heart sound with a loud P2, pan-systolic murmur of grade 4 in lower left parasternal area and a diastolic murmur of grade 2 in pulmonary area.

Electrocardiogram showed atrial flutter with a fixed 4:1 block along with right ventricular hypertrophy and right axis deviation. (Figure 2)

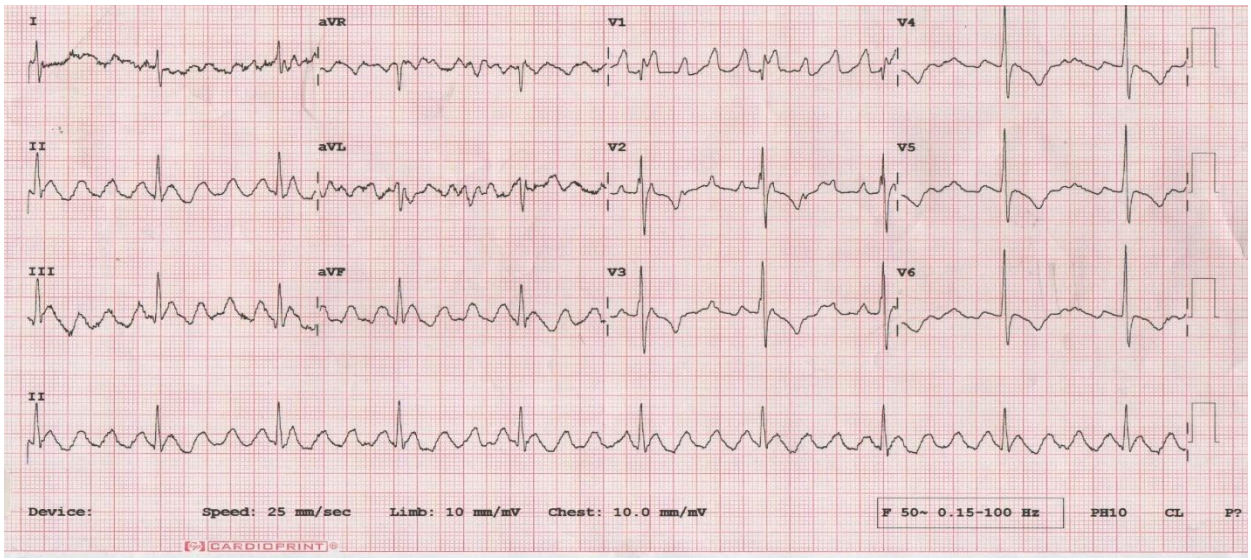

Figure 2: ECG showing Right Axis Deviation, RVH and Atrial Flutter with 4:1 block.

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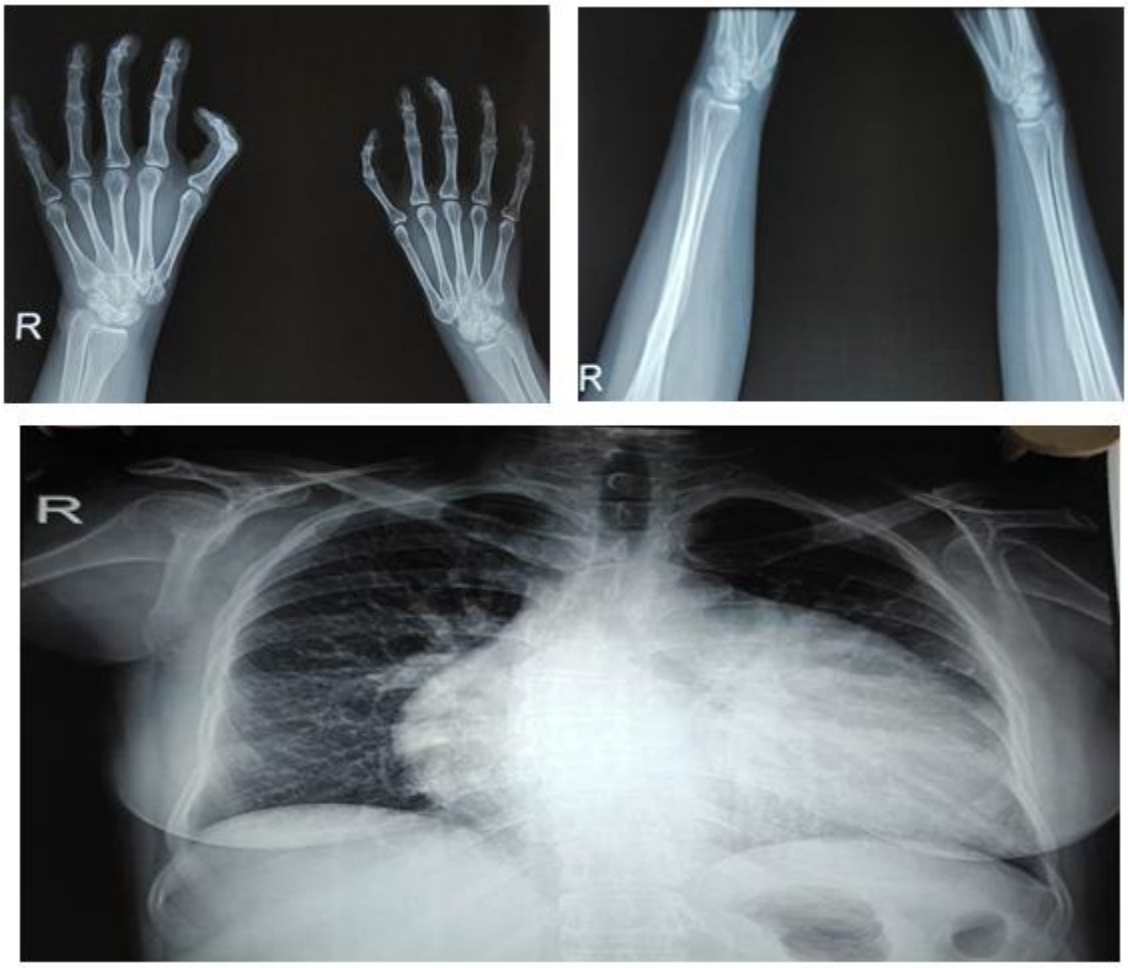

Figure 3. X-ray films of the hands, forearms showing Fingerisation of Thumbs and Fused carpal bones and Chest X Ray PA view showing Cardiomegaly.

Transthoracic Echocardiogram was performed which revealed dilated right sided cardiac chambers, dilated Pulmonary artery with an ostium seccundum type of atrial septal defect. Color doppler revealed a moderate to severe tricuspid regurgitation, mild to moderate pulmonary regurgitation. (Figure 4)

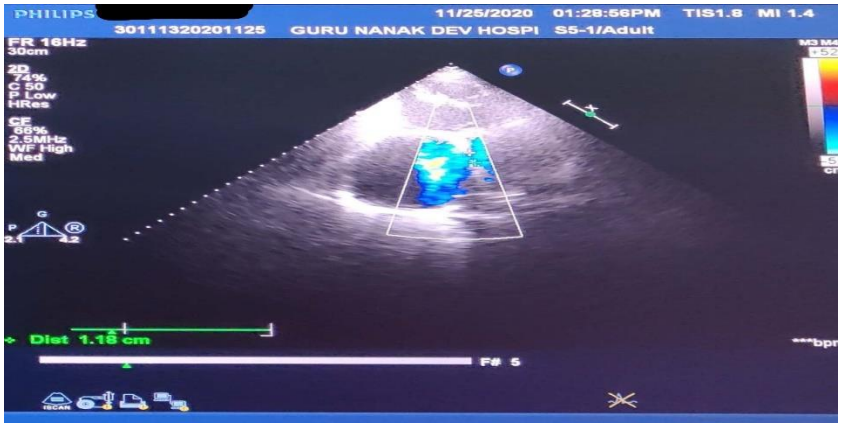

Figure 4: Trans Thoracic Echocardiography showing ASD

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Discussion:

Holt–Oram syndrome (HOS) comprises of congenital abnormalities involving the upper limbs and heart. It is caused due to a single-gene *TBX5* "protein-producing" mutation with gene map locus 12q24. It has autosomal dominant mode of inheritance. It was first described in 1960 by Holt and Oram.[1] Although, it can be detected intrauterine during the anomaly scan presenting as abnormal upper-limb development, it is usually detected after birth.[2]

The clinical diagnostic criteria of HOS are personal and/or family history of cardiac septation and/or conduction defects in the setting of preaxial radial ray axis deformity.[3]

Skeletal deformities may include having a missing thumb, a long thumb that looks like a finger, partially or completely missing bones in the forearm or upper arm and problems with the shape of the collar bone or shoulder blades.[4]Abnormalities are usually asymmetric. Left-side hand and arm are involved more commonly than the right-side. Lower limbs are rarely involved because the mutant gene interferes with the embryonic differentiation during the 4th and 5th weeks of pregnancy, when the lower limbs are not differentiated.[5]

The congenital heart defects are present in more than 85% of affected individuals particularly having atrial septal defect. ASD is of ostium seccundum type in majority of cases. Ventricular septal defects that can be associated with other cardiac anomalies like mitral valve prolapse, pulmonary stenosis and arrhythmia in the form of atrioventricular block have also been reported. [6]

Chest X ray usually shows cardiomegaly, Enlarged pulmonary arteries or evidence of congestive heart failure

Electrocardiogram usually shows rhythm abnormalities in form of atrioventricular conduction defects, atrial flutter, atrial fibrillation

Echocardiography is procedure of choice to detect abnormalities in heart like ASD and VSD

Genetic testing for TBX5 gene located on chromosome no 12q24.1 can be done. However, at present this only attributes to confirmation of diagnosis. No prognosis has been advised using this gene.

However, the patient can be offered treatment prior to development of complications secondary to cardiac defect. The skeletal deformities are hence a window to visceral abnormality. Early recognition and risk stratification can enhance patient care and provide benefit in terms of symptoms and complication free life.

However, treatment of HOS is individualized and based on specific symptoms. Medications to consider depending on the specific cardiac defects. Upper limb abnormalities may require corrective or reconstructive surgery in addition to physical and occupational therapy.

Conclusion:

We evaluated a patient having Morphological Upper Limb deformities since birth and now she developed Cardiac symptoms since last few days and seeking treatment for the same.On evaluation we found Atrial flutter with 4:1 block with Ostium seccundum type of ASD and Bilateral Fingerisation of Thumb and Carpal bone fusion. Above features suggestive of a rare congenital syndrome named Holt Oram Syndrome that went undiagnosed until latter in life.

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