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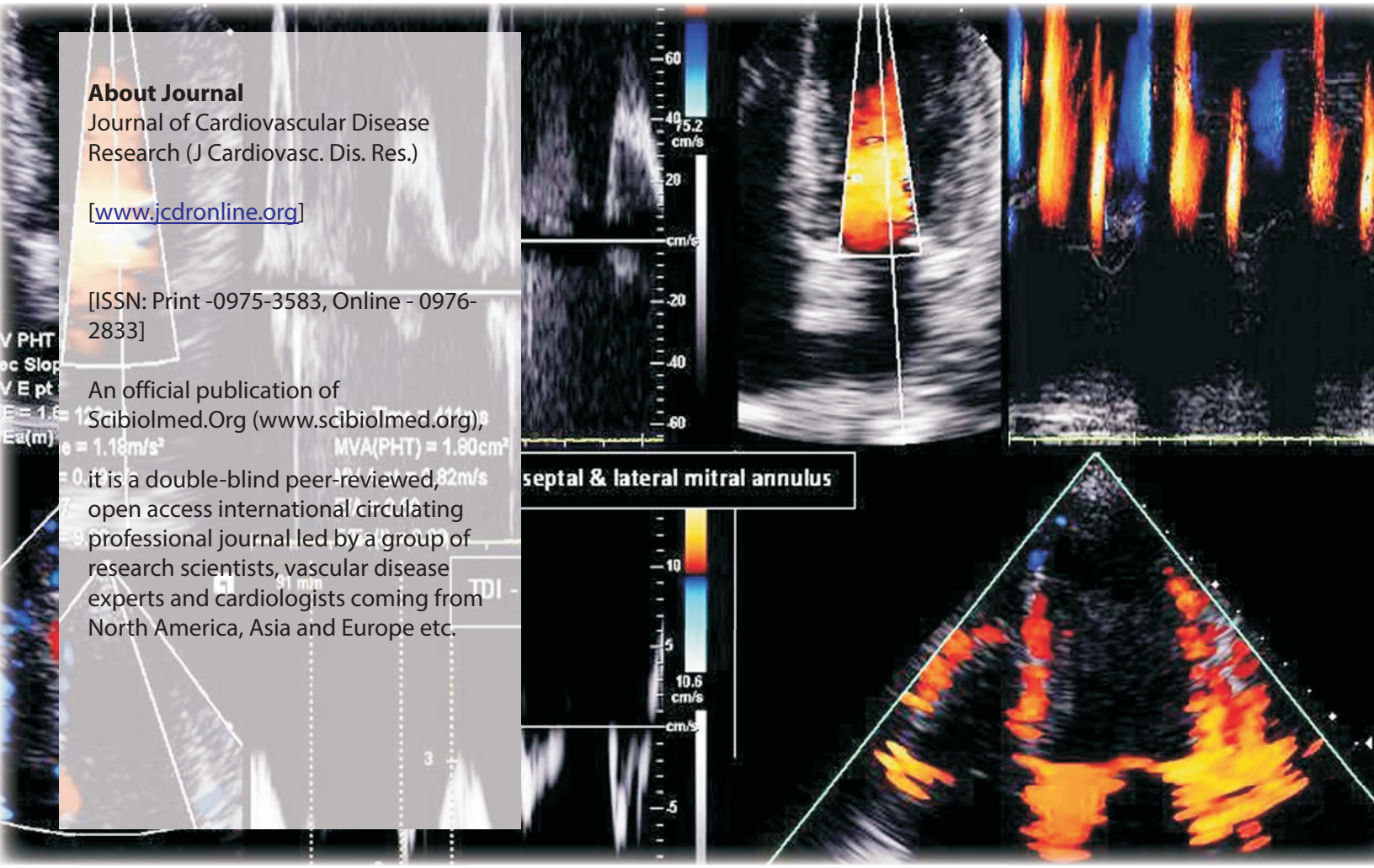

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Case Report

The Classical Holt Oram Syndrome

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ABSTRACT

We report a case of 2 year old female child who was referred to cardiology out-patient department with congenital left upper limb deformity. On examination she had a small forearm with radial deviation of hand and hypoplasia of four fingers. On retrospective evaluation she was found to have repeated respiratory tract infection. Chest roentgenogram revealed cardiomegaly and echocardiogram revealed a 10-11 mm Atrial septal defect (ASD) with left to right shunt. In view of limb deformity, she underwent soft tissue release followed by JESS fixator application and distraction. We emphasise the importance of syndromic diagnosis in all paediatric cases presenting with limb abnormalities.

Key words: Holt Oram syndrome, Atrio-digital dysplasia, Heart-hand syndrome, Atrial Septal defect.

Key Messages: A syndromic diagnosis should be kept in mind in all the paediatric cases presenting with congenital upper limb deformities.

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INTRODUCTION

Holt Oram syndrome (HOS) first described in 1960 is an Autosomal dominant disorder with complete penetrance. It is also known as Atrio-digital dyplasia and Heart-Hand syndrome. It is characterized by a triad of congenital cardiac anomalies, Cardiac conduction defects and hand malformation. It is seen in 1 in 100,000 live births. Till now 300 case reports have been published with varied manifestations. Here we report a case of 2 year old child referred to cardiology out patient department with congenital left upper limb deformity and diagnosed to have Holt Oram syndrome.

CASE HISTORY

A 2 year old female child was referred to orthopaedic department of our hospital with congenital malformation of left hand. She was a single child, born out of a non-consanguineous marriage. There was no family history of similar condition. Her developmental milestones were normal. In view of repeated upper respiratory infections, she was diagnosed to have a cardiac defect and was on regular check up with the cardiologist. Her general physical examination showed small forearm, radial deviation of hand with hypoplasia of 4 fingers with absent thumb on the left side. There was ulnar bowing of the forearm with increased web space between 2nd and 3rd fingers. On palpation single bone felt in left forearm. There were minimal movements at the metacarpo-phalangeal joints with no active movements at the left elbow and wrist (Figure 1a and 1b). X -ray of left upper limb showed absent thumb bones and radius with shortened ulna and elbow dislocation (Figure 2). Cardiac evaluation was sought to rule out underlying cardiac anomalies which showed ejection systolic murmur in tricuspid area with left parasternal heave. Electrocardiogram showed right axis deviation with evidence of right ventricular hypertrophy and incomplete right bundle branch block (Figure 3). Chest X-ray showed cardiomegaly (Figure 4). Echocardiogram revealed a 10-11 mm ostium secundum ASD with left to right shunt with an intact interventricular septum and no evidence of other congenital anomalies (Figure 5). She underwent soft tissue release and JESS fixator application followed by distraction.

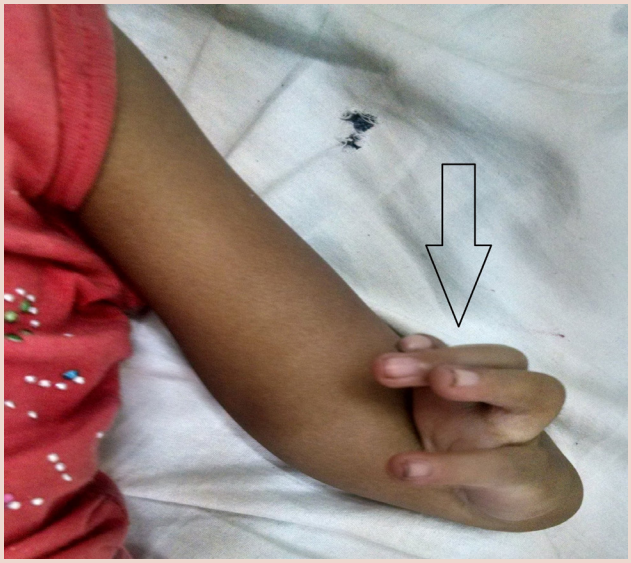

Figure 1a: Figure showing Radial deviation of hand with hypoplasia of four fingers with absent thumb on the left side &. ulnar bowing of the forearm with increased web space between 2nd and 3rd fingers

DISCUSSION

Holt Oram syndrome first described in 1960 is an Autosomal dominant disorder with complete penetrance. It is also known as Atrio-digital dyplasia and Heart-Hand syndrome. It is characterized by a triad of congenital cardiac anomalies, cardiac conduction defect and hand malformation. 40% cases are sporadic. Mutations in T-Box genes, namely TBX3 and TBX5 located on chromosome 12q12 are responsible for the varied phenotypic manifestations. These two genes play an important role in cardiac and skeletal development.[1]

TBX5 acts synergistically with NKX2-5 binding to the promoter of the gene encoding cardiac-specific natriuretic peptide precursor Type

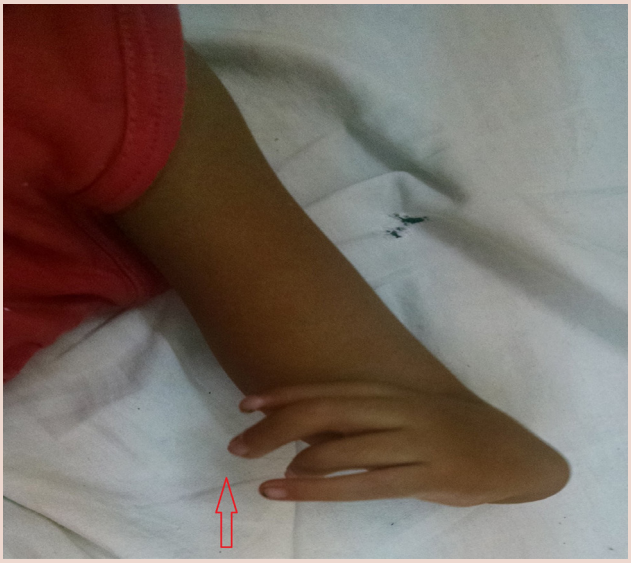

Figure 1b: Figure showing Radial deviation of hand with hypoplasia of four fingers with absent thumb on the left side &. ulnar bowing of the forearm with increased web space between 2nd and 3rd fingers.(Different view)

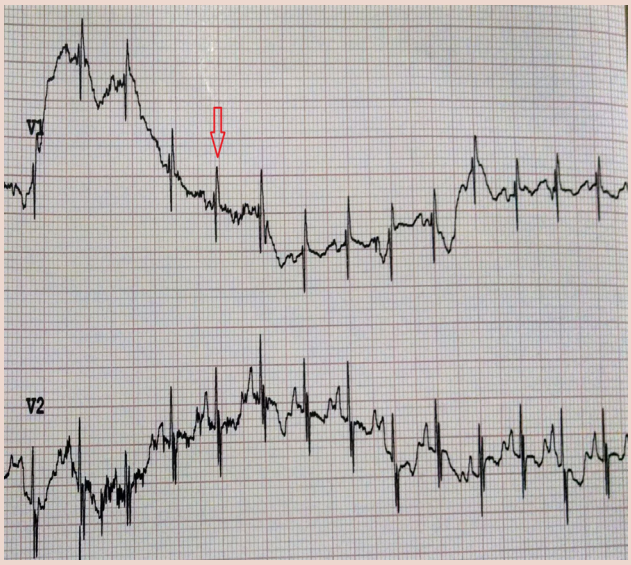

Figure 3: Electrocardiogram showing leads V1 and V2 demonstrating incomplete right bundle branch block. PS:Baseline artifacts are present as the child was moving while taking the ECG

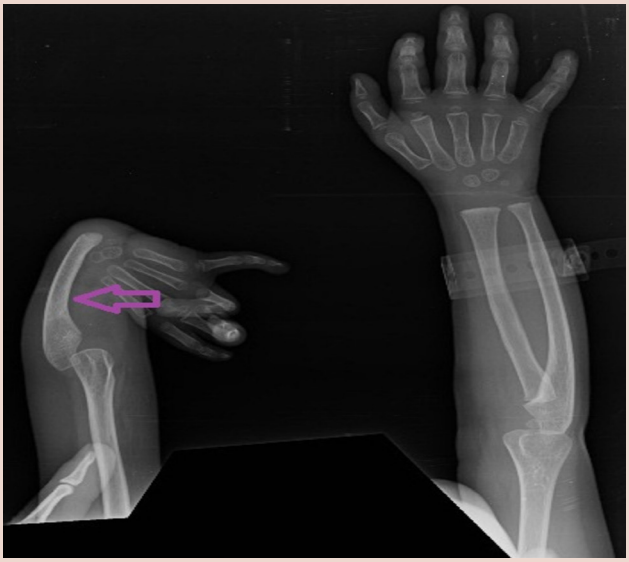

Figure 2: Figure showing absent radius and thumb with shortened ulna and dislocated elbow

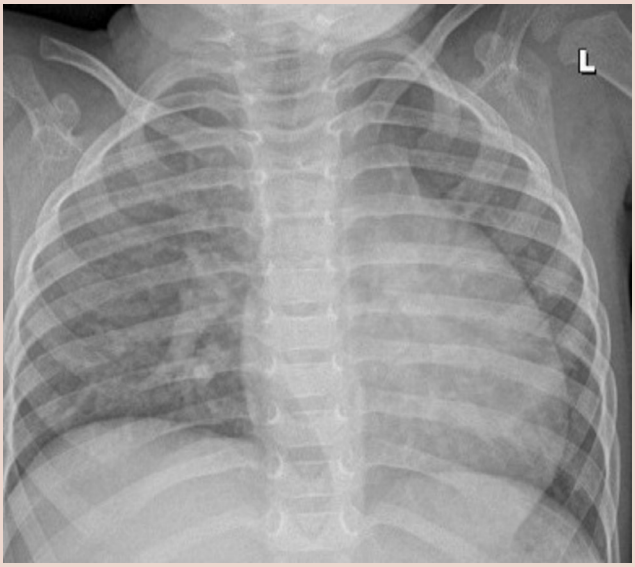

Figure 4: Chest X-ray PA view showing cardiomegaly with pulmonary plethora

A (NPPA) and promote cardiac myocyte differentiation. Mutations in these two T-box genes is responsible for the varied cardiac manifestation and limb defects seen in HOS.[1] The most common cardiac abnormality include Ostiumsecundum ASD accounting for 60% of the cases of the HOS, followed by VSD.In a study by S.Shono ,K.Kumano.K.Higa,K.Dan ASD accounted for 41.8% followed by VSD accounting for 13.8%. Other cardiac abnormalities include PDA, hypoplastic left heart, total anomalous pulmonary venous return, endocardialcushion defects, truncus arteriosus.[2] TBX5 mutations are present in 74% of the cases who meet the diagnostic criteria of presence of preaxial radial ray malformation of atleast one upper limb along with a personal or a family history of septation defects and/or atrioventricular conduction disease.

Connexin 40, a target of transcription factor TBX5 is required for normal cardiac conduction.Mutation of TBX5 result in varied cardiac conduction defects such as paroxysmal tachycardia, prolonged PR interval,wandering atrial pacemaker, atrial ectopics,atrioventricular and sinus bradycardia, right bundle branch block, sinus arrest and wolf Parkinson syndrome.

Skeletal abnormalities mainly includes thumb which can be absent, hypoplastic or triphalanged and is associated with hypoplastic thenar or limited supination of forearm. Other skeletal abnormalities include abnormal position of thumb, forearm and shoulder, underdevelopment or absence of forearm bone. Newbury-Ecob *et al.* (1996) reported a cohort of patients with limb defect. Absence of thumb was found in

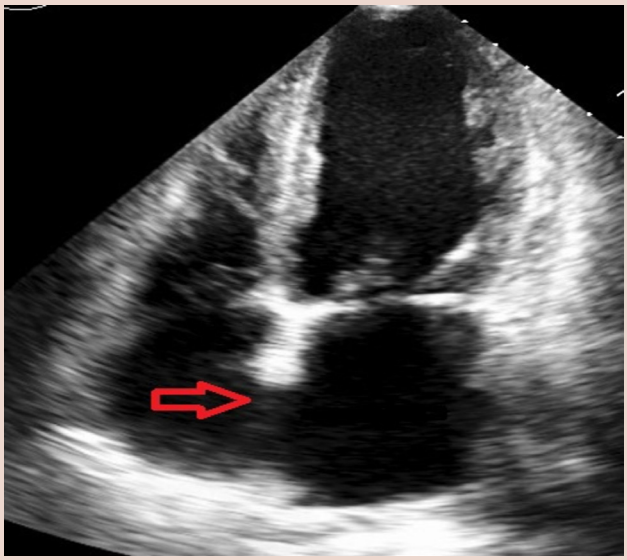

Figure 5: Echocardiogram in apical 4 chamber view showing a 10-11 mm atrial septal defect

19 cases and radius was absent in 10 cases.[3] However there is no mention as to of the number of patients having both these defects as in our case.

The case we presented appears to be sporadic, as the parents did not have any features of Holt Oram syndrome and the patient did not have any first degree sibling. However in view of inaccessibility to the patient we were unable to do genetic testing.

Diagnosis of Holt Oram is based on careful physical examination and family history. Upper limb skeletal defect can be visualized on X-ray. Electrocardiogram and Echocardiogram are required to diagnose the Conduction defects and cardiac malformations. Molecular genetics, though not available at all places can be used for confirmation of the disease. Prenatal echocardiography can be used to detect the cardiac malformations in the affected parents.

Treatment depends on the management of specific symptoms. Upper limb defects can be treated with corrective or reconstructive surgeries or artificial prosthetics. In patients with mild cardiac conduction defects, no treatment is required. Patient with severe cardiac conduction defects may require pacemaker. Structural abnormalities of heart to a certain extent can be corrected with surgeries or catheters. Antibiotics should be prescribed before surgical procedures in certain individuals with cardiac defects who are at risk for infective endocarditis.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

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