Holt–Oram Syndrome: Hands are the Clue to the Diagnosis

Abstract

Holt–Oram syndrome or heart–hand syndrome consists of phenotypic and genotypic abnormalities. It is characterized by abnormalities of upper limbs and congenital cardiac defects. It is an autosomal dominant disorder due to a mutation in TBX5 gene located on chromosome 12, but sporadic cases have also been reported. We describe a 26-year-old female with a history of shortness of breath for 5 years. She had bilateral hand deformities, and on evaluation, found to have ostium secundum atrial septal defect which is common cardiac defect in Holt–Oram syndrome.

Keywords: *Atrial septal defect, Holt–Oram syndrome, TBX5 gene*

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Introduction

Holt–Oram syndrome is characterized by morphological abnormalities of upper limbs and cardiac defects. The name was given by Dr. Mary Holt and Dr. Samuel Oram in 1960 in a four-generation family with atrial septal defects (ASDs) and thumb abnormalities.[1,2] Our patient had bilateral hand deformities along with congenital cardiac defect. Similar hand deformities were present in her child with no cardiac defects.

Case Report

We present a case of a 26-year-old female born through nonconsanguineous marriage belonging to lower socioeconomic status, with having bony defects of both upper limbs since birth. She had polydactyly (five fingers) with absent thumb [Figure 1]. She complained of having dyspnea on exertion class II for 5 years and was evaluated in multiple primary care hospital and subsequently referred to a tertiary care center. There was no history of congestive cardiac failure, angina on exertion, pedal edema, and paradoxical embolism. Clinical examination was suggestive of loud S1, wide, and fixed split-second heart sound and ejection systolic murmur of grade 3/6 at pulmonary area. The electrocardiogram [Figure 2] showed normal sinus rhythm, first-degree atrioventricular (AV) block with PR of 240 ms, incomplete right bundle branch block, and diffuse reperfusion abnormalities. Chest X-ray [Figure 3] showed cardiomegaly, prominence of the main pulmonary artery, and increased pulmonary vascularity. The transthoracic echocardiogram in the parasternal long-axis view [Video 1 - Link available in the online version] and apical four-chamber view [Figure 4] showed dilated right atrium, right ventricle, and 13 mm caudally shifted ostium secundum (OS-ASD) with left to right shunt. She was advised for surgical closure of ASD, but due to financial constraints, surgery could not be done. She was on medical management and is doing well in follow-up at 2-year follow-up.

On family screening, all family members were normal except her child who had similar hand deformities. Echocardiography was done which did not reveal any cardiac defect. She was explained about her disease and risk of transmission of congenital heart disease in further pregnancy.

Discussion

Holt–Oram syndrome, also called as atriodigital dysplasia, is a rare autosomal dominant syndrome with a prevalence of 1/100,000 in the Western population.[3-5] Most of the patients had a genetic inheritance; sometimes, sporadic cases were also reported in the literature.[6,7] There is phenotypic and genetic variation in patients of Holt–Oram syndrome as some patients present with mild hand deformities only and remain asymptomatic throughout

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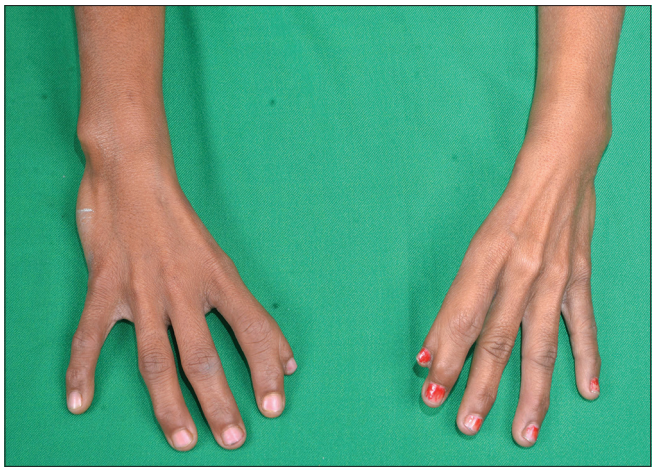

Figure 1: Polydactyly (five fingers) with absent thumb

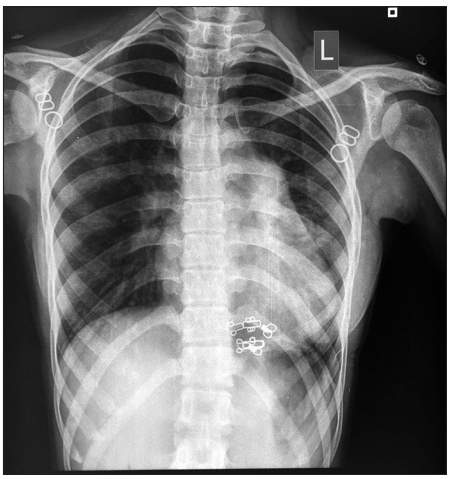

Figure 3: Chest X-ray showed cardiomegaly, prominence of the main pulmonary artery, and increased pulmonary vascularity

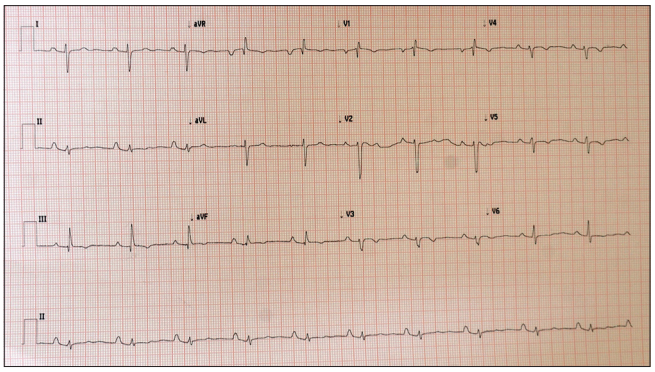

Figure 2: The electrocardiogram showed normal sinus rhythm, first-degree atrioventricular block with PR of 240 ms, incomplete right bundle branch block, and diffuse repolarization abnormalities

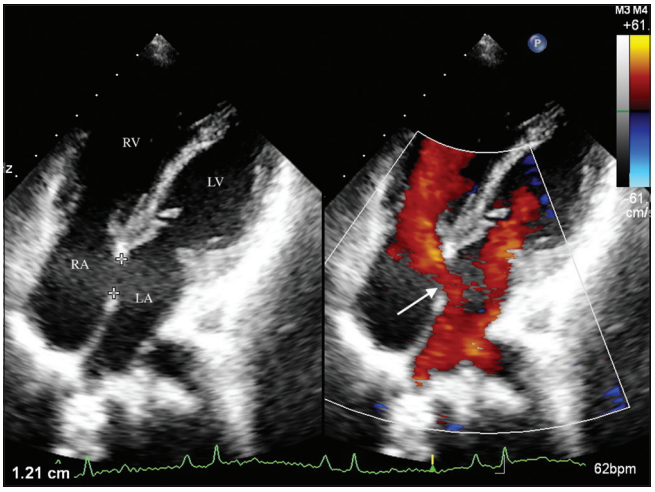

Figure 4: Two-dimensional echocardiography (apical four-chamber view with color compare) showing 12.1 mm ostium secundum atrial septal defect with left to right shunt

their life. TBX5 gene mutation is seen in 74% of clinically detected cases.[8] TBX5 is a T-box containing transcription factor involved in forearm and heart development. Genetic analysis showed nonsense mutations, deletions, rearrangements, and missense mutations in the TBX5 gene. Different mutations lead to variable expression of a gene which lead to phenotypic malformation.[4]

The characteristic malformation in the upper limb is the absent, underdeveloped, or triphalangeal thumb. There are malformations of the metacarpals, hypoplastic or absent radii, ulna, or humerus. Malformations can be unilateral or bilateral and symmetric or asymmetric. Embryologically, it is due to defective development of embryonic radial axis that results in variable deformities in the upper limb.[1] The scapulae may be absent and hypoplasia of the glenoid cavity. Upper limb abnormalities are always present, and the presence of lower limb abnormalities excludes the diagnosis.[3]

The various cardiac defects associated with Holt–Oram syndrome are ASDs, ventricle septal defects (VSDs), patent ductus arteriosus, endocardial cushion defects, hypoplasia of left ventricle, and pulmonary stenosis.[1] Common cardiac defects are OS-ASD and VSDs.[1,6] Conduction disturbances sometimes associated with Holt–Oram syndrome such as first-degree AV block, sinus bradycardia, wandering pacemaker, and atrial fibrillation.[9-11]

Conclusion

Hand deformities sometimes give us a diagnosis of congenital heart disease. Even in sporadic cases of Holt–Oram syndrome, screening of siblings should be done by echocardiography as these patients have more chances of transmission of congenital heart disease to siblings when compared with the normal population.

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Conflicts of interest

There are no conflicts of interest.

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