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Holt–Oram Syndrome Associated with Complex Congenital Heart Disease: A Rare Case Presentation and Literature Review

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Abstract

BACKGROUND: First described by Holt and Oram in 1960 in a four-generation family with atrial septal defects and thumb abnormalities, is an inherited disorder characterized by abnormalities of the upper limbs and heart. This syndrome is characterized by upper extremity malformations involving radial, thenar, or carpal bones. An abnormal carpal bone is present in all affected individuals and may be the only evidence of disease. About 75% of individuals with Holt–Oram syndrome (HOS) have a congenital heart malformation which may include an atrial or ventricular septal defect or heart block. In rare cases, the syndrome can affect other organs and systems which can be life threatening.

CASE REPORT: Here, we present a newborn with clinical and radiologic features of HOS consisting of bilateral asymmetric hypoplastic thumbs, generalized brachydactyly, limited bilateral supination due to radioulnar synostosis, and associated with complex heart disease and hypoplastic tricuspid valve.

CONCLUSION: In our case HOS is associated with complex congenital heart defects including atrial septal defect, ventricular septal defect with hypoplastic tricuspid valve. Based on the listed literature we didn't find any other case where tricuspid valve was affected.

Introduction

Holt–Oram syndrome (HOS) (also called an atriodigital syndrome, atriodigital dysplasia, cardiac-limb syndrome, heart-hand syndrome type 1, HOS, and ventriculo-radial syndrome) is an autosomal dominant very rare disorder that affects bones in the arms and hands (the upper limbs) and often causes heart problems [1]. HOS is the most common of the heart-hand syndromes with the estimated prevalence between 0.7 and 1/100,000 births. HOS has been reported from a number of countries worldwide and in individuals of different racial and ethnic backgrounds [2]. Bone abnormalities may affect only one side of the body or both sides; if both sides are affected differently, the left side is usually affected more severely. About 75% of individuals with HOS also have congenital heart problems, with the most common being defects – atrial or ventricular septal defect (VSD) [3]. The most common problem is ostium secundum atrial septal defect (ASD) and VSD, especially those occurring in the muscular trabeculated septum and cardiac conduction disease. So far, no signs of heart valve disease have been reported.

Case Report

A mail newborn weighing 3200 g from the normal pregnancy and normal delivery at 39 weeks of gestation was done. At the delivery, the baby was normal with an Apgar score of 8 and 9 at 1 and 5 min, respectively, and a SaO_2 level of 92%. The previous family medical history was unremarkable, and there was no family history of congenital malformation. During pregnancy by the obstetrician, some routine echosonographic examinations have been made, and no any morphological or heart disease has been referred. During the first postnatal routine clinical examination, complex morphological deformities of upper extremities have been registered. Both auricles of the ear were deformed with the normal external canal (Figures 1 and 2). Furthermore, hypospadia Grade I and right reponible inguinal hernia were noted (Figure 3). The chest X-ray was normal (Figure 4). The electrocardiogram presented normal sinus rhythm, right axis deviation, and incomplete block of the right bundle branch. Routine X-ray of upper extremities showed bilateral and symmetric upper limb malformations which include unequal

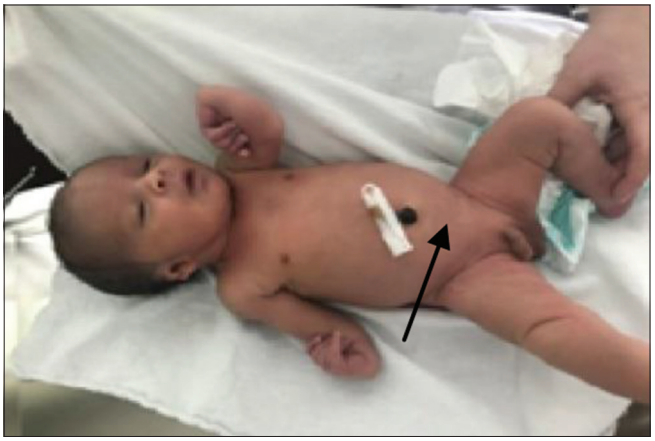

Figure 1: Deformities of upper extremities and inguinal hernia

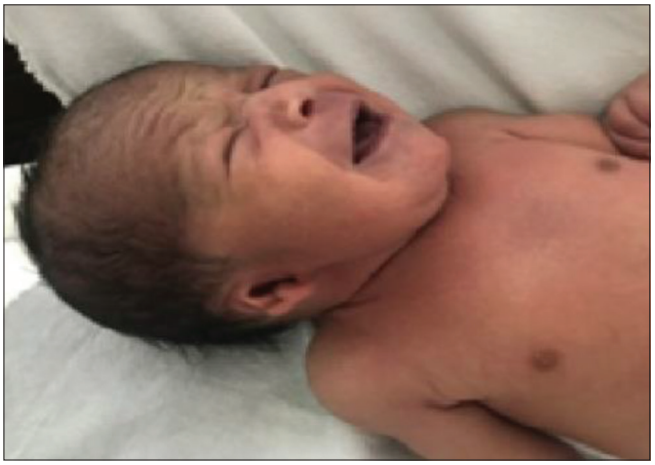

Figure 2: Deformities of ear auricles

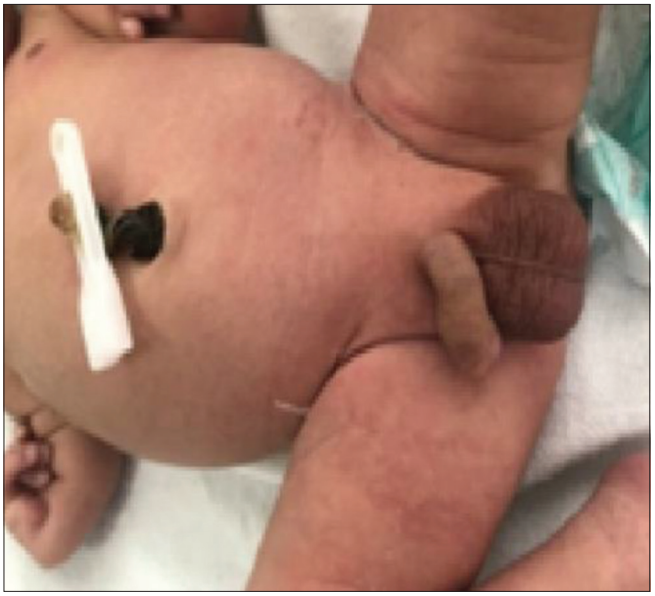

Figure 3: Reponible inguinal hernia

arm length caused by aplasia of the both radius, anomalous development of the carpal and thenar bones, abnormal forearm pronation and supination, abnormal opposition of the thumb, and sloping shoulders and restriction of shoulder joint movement (Figures 5-8).

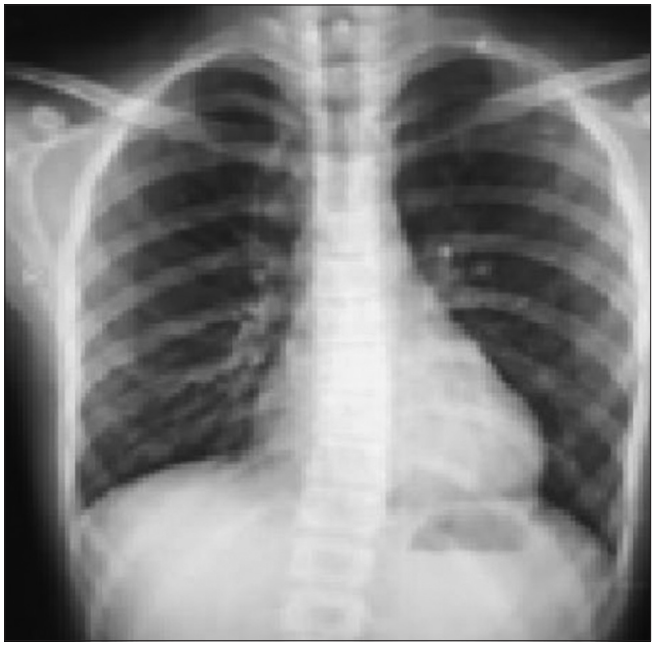

Figure 4: Normal X-ray Chest

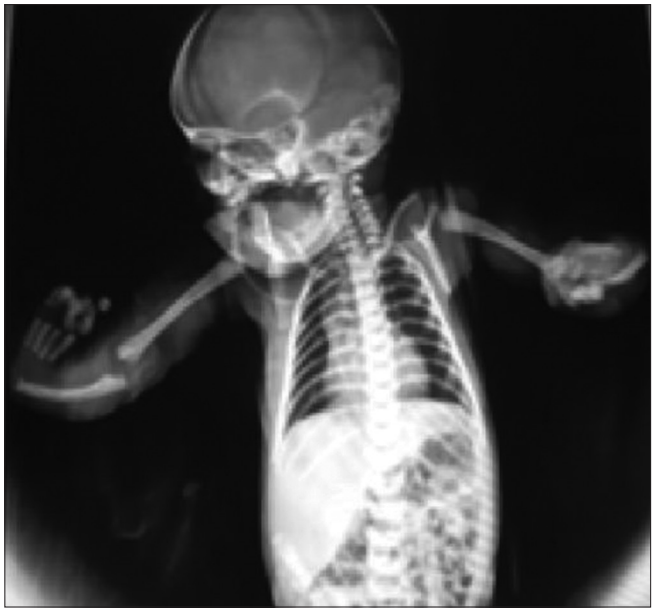

Figure 5: Multiple upper limb malformations

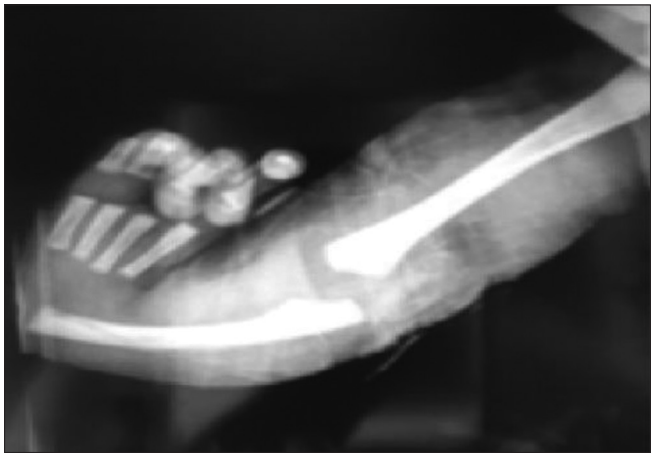

Figure 6: Multiple upper limb malformations

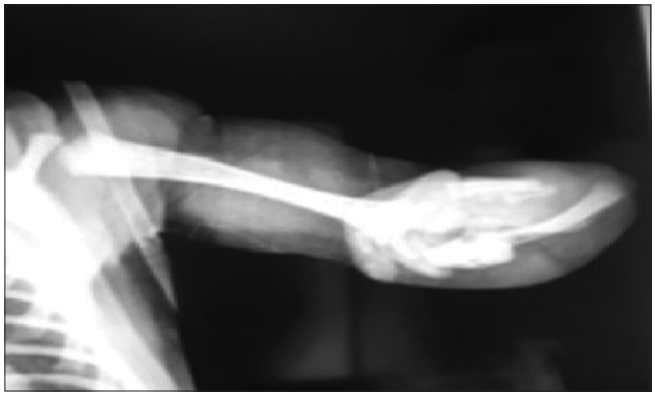

Figure 7: Multiple upper limb malformations

Transthoracic echocardiography showed normal situs of the thoracoabdominal organs and normal pulmonary and systemic venous return. The interatrial septum is largely absent mimicking the anatomy of common atrium with a bidirectional shunt. Mitral valve was normal, with normal anterograde flow, while the tricuspid valve was mostly presented as a continuous fibrotic tissue with hypoplastic tricuspid valve in a central position, measuring 2–3 mm in diastole, causing restrictive anterograde flow and trivial systolic regurgitation. The tricuspid valve was very tight, showing all hypoplastic leaflets with extremely restrictive anterograde flow. Furthermore, transthoracic echocardiography presented at the subaortic part of interventricular septum a non-restrictive VSD with bidirectional flow. The aorta was normal, while pulmonary valves were stenotic, causing turbulent anterograde flow during the systole with maximal speed of 3.8 m/s and 58 mm of mercury. The pulmonary trunk and right pulmonary branch were normal while the left pulmonary artery was hypoplastic at the level of origin. Other heart structures were normal (Figure 9). During examination, normal heart rhythm was noted.

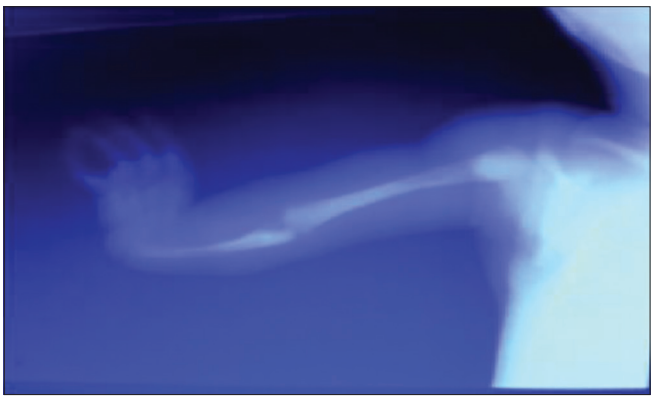

Figure 8: Multiple upper limb malformations

Genetic testing showed a new (*de novo*) mutations in the TBX5 gene. After 1 month, the routine examination was done, and normal growth and development for age was ascertained (Figure 10).

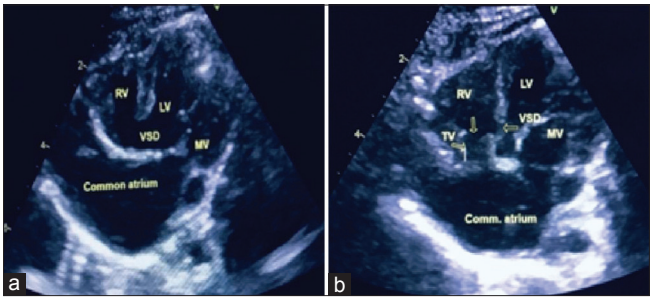

Figure 9: Transthoracic echocardiography in systole (a) and in diastole (b)

Discussion

HOS was named as a sign of respect to Mary Holt and Samuel Oram, who published a paper on it in 1960 [3]. The syndrome is unique and characterized by upper limb defects, congenital heart malformation, and cardiac conduction disease. HOS is the most common of the heart-hand syndromes. The estimated prevalence of HOS is between 0.7 and 1/100,000 births [4].

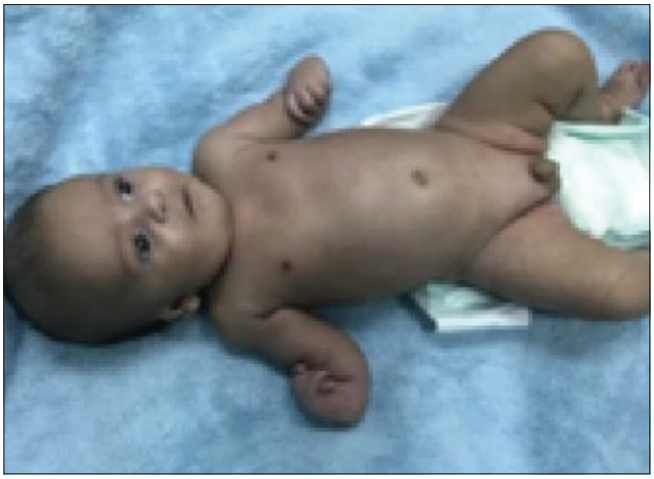

Figure 10: Condition after 1 month of age

The symptoms and physical findings associated with HOS vary greatly from person to person, even within the same family. Bone abnormalities associated with the syndrome otherwise vary widely in severity and include a missing thumb, a thumb that looks such as a finger (triphalangeal thumb), upper arm bones (humerus) of unequal length, partial or complete absence of bones in the forearm, an underdeveloped humerus, and abnormalities in the collar bone (clavicle) or shoulder blade (scapula) [1]. Bone abnormalities may affect only one side of the body or both sides; if both sides are affected differently, the left side is usually affected more severely [2]. In our case, bone abnormalities have affected both sides, including symmetrically absent radius, but the left upper limb is more severely affected.

HOS is inherited in an autosomal dominant manner. Approximately 85% of affected individuals have HOS as the result of a *de novo* pathogenic variant. Offspring of an affected individual is at 50%

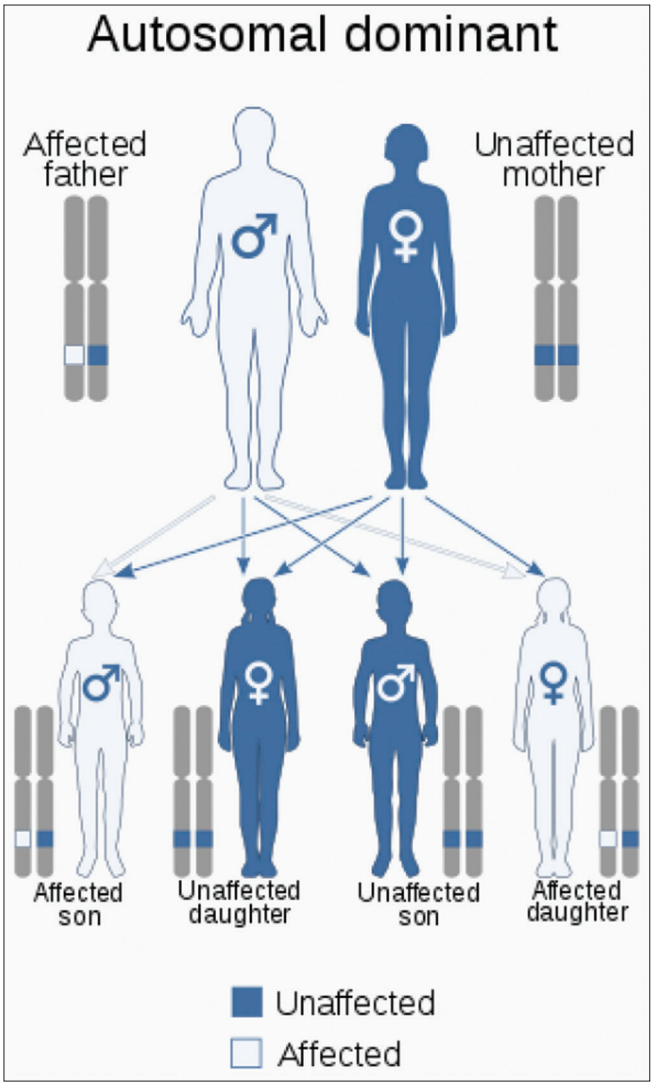

Figure 11: Affected individuals in HOS

risk of being affected (Figure 11). In pregnancies at 50% risk, detailed high-resolution prenatal ultrasound examination may detect upper limb malformations and/or congenital heart malformations [5]. Prenatal molecular genetic testing may be used to confirm a diagnosis if the *TBX5* pathogenic variant has been identified in affected relatives. Furthermore, clinical diagnostic criteria for HOS have been established and validated through molecular genetic testing. The diagnosis of HOS is established in a proband with a preaxial radial ray anomaly and a personal or family history of cardiac septation and/or conduction defects. More than 70% of individuals who meet strict clinical diagnostic criteria have an identifiable heterozygous pathogenic variant in *TBX5* [6]. In our case, despite the fact that some routine echosonographic examinations by local obstetricians have been made, no any malformations in the hands or in the heart have been noted.

A congenital heart malformation is present in 75% of affected with HOS and most commonly involve the atrial or/and ventricular septum. ASD and VSD can vary in number, size, and location. ASDs can present as a common atrium and are often associated with cardiac chamber isomerism, left or right which even more complicates the clinical picture and future [7]. In this aspect, our case is unique because he has a large ASD mimicking a common atrium, large subaortic VSD, and hypoplastic tricuspid valve. In the recent published literature, we have not found any case with this heart complex.

Some individuals with severe congenital heart malformation may require surgery early in life to repair significant septal defects. Other individuals may have complex congenital heart malformations while conotruncal malformations, though observed in HOS, are not common and may be caused by other genetic defects [8].

Children affected with HOS with or without a congenital heart malformation are at risk for cardiac conduction disease. While individuals 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 [9]. In our case, we did not find any heart rhythm disturbances even though the baby is very small, and during the next childbirth period, she could different rhythm disorders.

Conclusion

Holt–Oram syndrome is an autosomal dominant very rare syndrome that affects bones in the arms and hands. In most cases syndrome is associated with congenital heart disorders which can predominate in clinical presentation. In our case HOS is associated with complex congenital heart defects including atrial septal defect, ventricular septal defect with hypoplastic tricuspid valve. Based on the listed literature we didn't find any other case where tricuspid valve was affected.

Ethical Approval

This report was approved by the Institutional Review Board at our clinical center, and both parents provided written informed consent.

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Authors' Contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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