

Two Unrelated Families of Holt–Oram Syndrome: Delayed Bone Age, Patent Ductus Arteriosus and Complex CHD as Unreported Features

Avadhesh Joshi¹, Jai Prakash Narayan², Pukhraj Garg³, Suchitra Narayan⁴

¹Resident, Department of Pediatrics, JLN Medical College, Ajmer, Rajasthan, India, ²Assistant Professor, Department of Pediatrics, JLN Medical College, Ajmer, Rajasthan, India, ³Senior Professor & Unit Head, Department of Pediatrics, JLN Medical College, Ajmer, Rajasthan, India, ⁴Assistant Professor, Department of Obstetrics and Gynecology, JLN Medical College, Ajmer, Rajasthan, India

Abstract

Holt–Oram syndrome is a rare autosomal dominant syndrome associated with congenital heart disease and various congenital musculoskeletal abnormalities. This syndrome is also known as heart hand, heart upper limb and upper limb cardiovascular syndrome. The diagnostic criterion includes abnormalities of thumb (triphalangia, hypoplasia or aplasia) and congenital heart disease. This syndrome caused by mutations on chromosome 12q24.1 that inactivate the TBX5 gene. We report two unrelated families of Holt–Oram syndrome with the mother being first affected in the family, followed by her children. Our patient had delayed bone age, patent ductus arteriosus, complex CHD as additional features, which have not yet been reported.

Key words: Delayed bone age, Holt–Oram syndrome, Patent ductus arteriosus, Unrelated families

INTRODUCTION

Holt–Oram syndrome is a known autosomal dominant hand heart syndrome first described by Mary Holt and Samuel Oram in 1960 and since then more than 350 case reported.^{1,2} The most important findings includes atrial septal defects (ASDs), ventricular septal defect (VSD), atrioventricular conduction abnormalities, vascular hypoplasia and upper limb musculoskeletal deformities.^{3,4} This syndrome caused by mutations on chromosome 12q24.1 that inactivate the TBX5 gene.⁵ The criteria for diagnosing this syndrome includes abnormalities of thumb (triphalangia, hypoplasia or aplasia) and congenital heart disease.³

CASE REPORT

Family 1

Mother was the first affected person in the family. She was married to an unaffected male. She had three affected children and one abortion. The first female expired at the age of seven, cause of death was not known. Second issue spontaneously aborted. The third issue is a female child, and fourth is male child (Figure 1).

Case 1

This mother came with her 8-year-old male child that was 4th issue of unrelated 40-year-old female and 45-year-old male. Weight and height of child were 14.4 kg and 116 cm. Patient was admitted with complaints of fever, cough, cold, chest pain and breathing difficulty since last 7 days. There was a history of palpitation, repeated chest infection and not gaining weight, abnormal deformed upper limb since birth. On examination, he had pallor, chest in drawing, and pulse rate of 110/min, respiratory rate of 24/min, liver 2/7 cm below costal margin, pectus excavatum, and short clavicle, abnormalities of scapula were present (Figures 2a and b, 3a and b). He had

Access this article online



www.ijss-sn.com

Month of Submission : 03-2015
Month of Peer Review : 04-2015
Month of Acceptance : 04-2015
Month of Publishing : 05-2015

Corresponding Author: Avadhesh Joshi, Department of Pediatrics, JLN Medical College, Ajmer, Rajasthan, India.
E-mail: Joshi. kmc@gmail.com



Figure 1: Family 1 Holt–Oram syndrome copy



Figure 4: Upper limb deformities Case 1 Family 1 Holt–Oram syndrome - copy



Figure 2: (a) short clavicle 2 – copy, (b) short clavicle - copy



Figure 5: Upper limb deformities Case 1 Family 1 - copy



Figure 3: (a) scapular abnormalities - copy, (b) scapula - copy

bilateral dysgenesis of the forearm and of thenar area, limitation of supination and pronation movements on both side, but more on the left side, deformed thumb and arachnodactyly on the right side (Figures 4 and 5). Auscultation of the chest revealed bilateral crepitation, wheeze, and the pansystolic murmur of grade 4+/6+

all over the precordium. Blood investigation showed a moderate degree of microcytic hypochromic anemia. X-ray chest showed cardiomegaly with bilateral infiltration (Figure 6). X-ray forearm and wrist showed only two carpal bones, abnormal first metacarpal on the right side (Figure 7). Electrocardiography showed right axis deviation and echocardiography showed left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH), and moderate pulmonary stenosis (PS), moderate PR, apical VSD (11.2 mm) moderate mitral regurgitation (MR), membrane in left atrium, large CS opening in RA, one another channel opening in right atrium.

Case 2

A 13-year-old girl was the elder sister of the above child and 3rd child of their parents. She had complaints of palpitation. On examination, she had absent thumb and forearm on the left side. Cardiovascular examination showed precordial bulge, wide fixed splitting of second heart sound with an

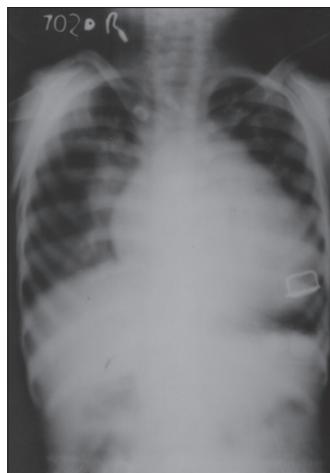


Figure 6: Holt-Oram Case 1 Family 1 cardiomegaly



Figure 8: Upper limb deformities Case 2 Family 1 - copy



Figure 7: Holt-Oram Case 1 Family 1 delayed bone age and upper limb bone deformities

ejection systolic murmur at the pulmonary area. X-ray chest showed cardiomegaly, and X-ray left forearm and hand showed absent forearm bones, 1st metacarpal and phalanges and only two carpal bones. ECG showed right bundle branch block with right axis deviation. Echocardiography showed ostium secundum ASD of 4 cm (Figure 8).

Case 3

A 38-year-old old patient was mother of above two children. She also had complaints of palpitation and history of repeated respiratory infection in childhood. On examination, she had short clavicle, on right side abnormal thumb while on left side absent thumb, increased gap between middle and ring finger, restricted movement at elbow and wrist on left side, difficulty in supination and pronation. Cardiac examination had grade 2nd murmur and echocardiography showed ostium primum ASD (Figure 9).

Family 2

The mother of the child was first affected in the family. She had a female child which was also affected (Figure 10).



Figure 9: Upper limb deformities Case 3 Family 1



Figure 10: Holt-Oram syndrome Family 2

Case 1

A 4-year-old female child was the daughter of 28 years old mother and 34 years old father and admitted with complaints of fever, cough, and breathing difficulty. She had bilateral abnormalities of thumb, thenar

hypoplasia, on both side there was increased gap between middle and ring finger and between the ring finger and little finger (Figures 11 and 12). There were restricted supination and pronation movements. There was mild precordial bulging. On cardiovascular examination the patient had no murmur. X-ray chest showed cardiomegaly and bilateral infiltration (Figure 13), X-ray forearm showed only two metacarpal bones (Figure 14). ECG showed right axis deviation and echocardiography showed large ASD and trivial patent ductus arteriosus (PDA).

Case 2

This 28-year-old female was the mother of the above child. She had no complaints but had right-hand thumb abnormalities and thenar hypoplasia while on left side thumb was absent. She had difficulty in supination and pronation movements. On cardiovascular examination, she had grade 2nd systolic murmur and echocardiography confirms ostium primum ASD (Figure 15).



Figure 11: Upper limb deformities Case 1 Family 2

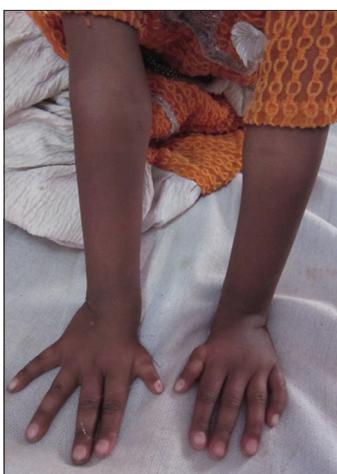


Figure 12: Upper limb deformities Holt-Oram syndrome Case 1 Family 2

DISCUSSION

In 1960 Mary Holt and Samuel Oram described this syndrome for the 1st time and since then different authors



Figure 13: Holt Oram syndrome Case 1 Family 2 cediomegaly



Figure 14: Upper limb bone deformities and delayed bone age



Figure 15: Case 2 Family 2 mother of Case 1 with hand deformities

have reported on approximately 350 patients.^{1,2} This syndrome is also known as heart hand, heart upper limb and upper limb cardiovascular syndrome.³ McKusick created the name Holt–Oram syndrome when describing a case in which a mother and her daughter were affected.⁶ The most frequent cardiac abnormalities are ASD of ostium secundum, VSD, ostium primum ASD and arrhythmias.^{1,3} Pulmonary arterial hypertension may occur in a significant number of patients and is generally a result of the excessive pulmonary blood flow caused by the ASD as in our case first in family one.³ Other rare cardiac abnormalities in this case are the presence of LVH, RVH, and moderate PS, moderate PR, apical VSD (11.2 mm) moderate MR, membrane in left atrium, large CS opening in RA, one another channel opening in right atrium which is not described in literature. In case one in family second, there was PDA along with ASD, a combination not yet described in literature.

Skeletal abnormalities spare the lower limbs. This occurs because the mutant gene interferes with the embryonic differentiation during the 4th and 5th week of pregnancy, when the lower limbs are not yet differentiated.¹ Our patients also had delayed bone age that is yet not described in literature as our patient had only two carpal bones

(Case 1 in family 1 and Case 1 in family 2). All other findings in our patients were as described by other author.¹⁻⁶

CONCLUSION

Many cases of Holt–Oram syndrome have now been reported from India but we would like to bring the attention toward the additional features that are to be looked in this syndrome *viz.* delayed bone age, PDA, complex CHD and scapular abnormalities.

REFERENCES

1. Holt M, Oram S. Familial heart disease with skeletal malformations. Br Heart J 1960;22:236-42.
2. Böhm M. Holt–Oram syndrome. Circulation 1998;98:2636-7.
3. Frota Filho JD, Pereira W, Leiria TL, Vallenas M, Leões PE, Blacher C, et al. Holt–Oram syndrome revisited. Two patients in the same family. Arq Bras Cardiol 1999;73:429-34.
4. Mogulevsky HC, O'Reilly MV, Dizadji H, Shaffer AB. Atrial septal defect associated with skeletal anomalies (Holt–Oram syndrome). Chest 1970;57:230-3.
5. Basson CT, Bachinsky DR, Lin RC, Levi T, Elkins JA, Soultz J, et al. Mutations in human TBX5 [corrected] cause limb and cardiac malformation in Holt–Oram syndrome. Nat Genet 1997;15:30-5.
6. Mackusick VA. Medical genetics 1960. J Chron Dis 1961;14:1-198.

How to cite this article: Joshi A, Narayan JP, Garg P, Narayan S. Two Unrelated Families of Holt Oram Syndrome: Delayed Bone Age, PDA and Complex CHD as Unreported Features. Int J Sci Stud 2015;3(2):240-244.

Source of Support: Nil, **Conflict of Interest:** None declared.