Acta Scientific PAEDIATRICS (ISSN: 2581-883X)

Volume 4 Issue 6 June 2021

Case Series

Case Series of Holt Oram Syndrome

Chakradhar Maddela*

Neonatologist, Associate Professor of Paediatrics, Prathima Institute of Medical Sciences, Nagunoor, Karimnagar, Telangana, India

***Corresponding Author:** Chakradhar Maddela, Neonatologist, Associate Professor of Paediatrics, Prathima Institute of Medical Sciences, Nagunoor, Karimnagar, Telangana, India.

Received: March 01, 2021

Published: May 15, 2021

Abstract

Pre-axial upper limb skeletal deformities involving thumb and radial bones are commonly associated with congenital cardiac defects. The common deformities are hypoplasia or aplasia of thumbs and radial bones. Skeletal involvement may be unilateral or bilateral. Atrial septal defect of ostium secundum is the most commonly associated congenital cardiac defect. Other possible cardiac defects are ostium primum variety of atrial septal defect, ventricular septal defects, patent foramen ovale and electric cardiac conduction abnormalities. The incidence is 1 in 1,00,000 live births. This syndrome involves TBX5 gene defect on long arm of chromosome 12. The most common inheritance pattern is autosomal dominant variety. New mutations are common. Antenatal detection by mid-trimester anomaly scan is possible.

Recently, we detected three cases of Holt Oram Syndrome at our health care facility during 2016 - 2019. These cases were presented with full spectrum of skeletal and cardiac defects in one case, near total expression in one case and partial expression of physical features in another case. Thumb abnormalities and cardiac defects involving atrial septal defect were found in all cases. All cases underwent second trimester anomaly scans but missed antenatal detection and lost potential antenatal counselling with parents.

Keywords: Heart Hand Syndrome; Thumb hypoplasia; Atrial Septal Defect (ASD); Forearm Skeletal Defects

Abbreviations

ASD: Atrial Septal Defect; OS: Ostium Secundum; LSCS: Lower Segment Caesarean Section; LUS: Lung Ultrasound Scan; hsPDA: Hemodynamically Significant Patent Ductus Arteriosus; PAH: Pulmonary Arterial Hypertension; RD: Respiratory Distress; TR: Tricuspid Regurgitation; USS: Ultrasound Scan

Introduction

Pre-axial upper limb skeletal deformities involving thumb and radial bones are commonly associated with congenital cardiac defects.

Case 1

A male baby of 37.3 weeks gestational age delivered by elective lower segment caesarean section (LSCS) to a gravida two mother with non-consanguineous marriage. Pregnancy was uneventful. APGAR scores were 7, 8, 9 at 1, 5, and 10 minutes. Baby brought by attendants for upper limb skeletal defects and mild respiratory distress.

Clinical features: Baby found in moderate respiratory distress with heart rate 158 beats per minute, SpO_2 93% in room air and showed bilateral upper limb skeletal deformities. Only three digits

were noticed with syndactyly in each hand. Both thumbs were absent bilaterally. Both hands showed thenar hypoplasia. Both wrists were unstable. No other skeletal anomalies found apart from upper limb deformities. A loud systolic heart murmur with thrill noticed on left lower parasternal area. No similar clinical findings were found in the family on both parents' side.

Infantogram: Whole body roentgenogram showed cardiomegaly with distinctly enlarged right atrial border and right ventricular cardiac apex. Radial bones were absent in both forearms, right and left. There were only three metacarpal bones in each hand. No carpal bones were noticed in both hands.

ECG: ECG findings suggestive of right atrial and right ventricular chamber enlargement noticed on ECG monitor during NICU stay.

Bedside echocardiogram: Two-dimensional echo showed 'D' loop heart with four chambers. Concordance noticed at atrioventricular and ventriculoarterial segmental level. Right atrium, right ventricle and pulmonary artery were enlarged. Atrial septal defect of ostium secundum (ASD OS) and ostium primum with endocardial cushion defects noticed. There was no left ventricular outflow obstruction. Colour Doppler showed a moderate size bidirectional hemodynamically significant patent ductus arteriosus (hsPDA). 2D Echo findings were confirmed on colour doppler. There was severe tricuspid regurgitation (TR) with pulmonary hypertension (PAH).

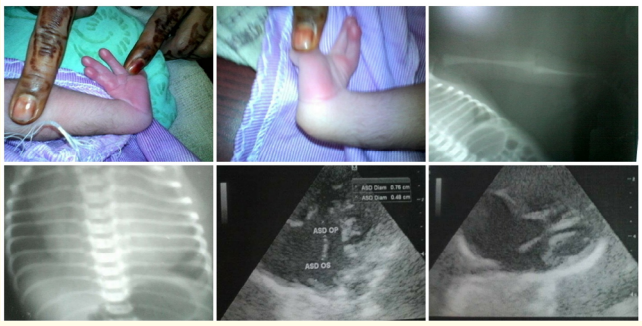

Figure 1: Upper row (from left to right) - a) Left hand and forearm with absent thumb, b) right hand and right forearm with absent thumb, c) x ray showing single forearm bone with absent radius. Lower row (from left to right) a) X ray chest showing cardiomegaly b) 2D Echo picture showing ASDs - ostium secundum and primum c) Echo picture showing grossly enlarged right atrium.

Bedside lung ultrasound: Lung ultrasound showed thickened pleura and confluent B lines suggesting wet lung pattern.

Genetic testing: This test was suggested but attendants refused for the same.

Management baby was admitted in neonatal intensive care unit (NICU) and given non-invasive respiratory support, pulmonary hypertension treated with milrinone, thermal care and nutritional support. Baby was discharged on day six on attendants request. At discharge, baby was accepting oral feeds with extracted mother's milk. Referrals to paediatric orthopaedic team and paediatric cardiology team were made for further management.

Case 2

A male term infant delivered by caesarean section to second degree consanguineous young parents in their first pregnancy. Baby's Apgar scores were normal at birth. Baby brought for physical deformities involving both hands and for mild respiratory distress. Physical examination showed mild respiratory distress, absent left thumb with thenar hypoplasia, incurving of fingers and short forearm.

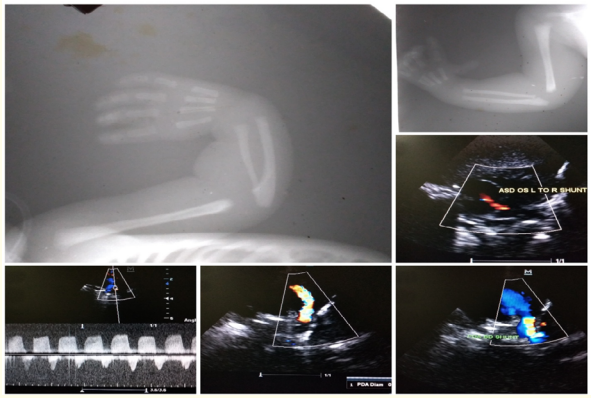

Figure 2: X ray left upper limb showing absent thumb, only four metacarpals, short forearm with hypo plastic left radial bone. X ray of right upper limb showing four metacarpal bones, hypo plastic right thumb attached to hand by skin only. The echo pictures from left to right showing pulse wave Doppler picture of bidirectional PDA, colour Doppler pictures showing turbulent flow, (left to right and right to left shunts), ASD -OS with left to right shunt.

Right upper limb showed hypo plastic thumb and mild hypoplasia of right radial bone. Chest x-ray revealed mild cardiomegaly with enlarged right atrial border. Bedside echo demonstrated ASD-OS with left to right shunt, hemodynamically significant PDA with bidirectional shunt and moderate TR with pulmonary hypertension. Lung USS showed wet lung pattern with sub pleural air-bronchogram. Blood chemistry revealed positive septic screen, elevated C reactive protein and procalcitonin levels suggesting early onset neonatal sepsis. Baby admitted and managed in NICU. PDA closed on day five. Baby received full course of intravenous antibiotics for seven days and discharged on day eight.

Case 3

A male term infant of non-consanguineous parents, delivered by caesarean section. Baby brought for congenital abnormality of right hand. Physical examination showed hypoplasia of right thumb with unstable wrist and thenar hypoplasia. Incurving of fingers were found in right hand. No other skeletal abnormalities were noticed except in right hand. Left hand thumb was normally developed. X ray of right upper limb showed presence of both forearm bones, four metacarpal bones and hypo plastic thumb. X ray of left upper limb showed normal forearm and hand bones. X-ray chest showed right atrial enlargement. Echocardiogram showed ASD ostium secundum type of moderate size. Baby managed on outpatient basis with paediatric orthopaedic referral.

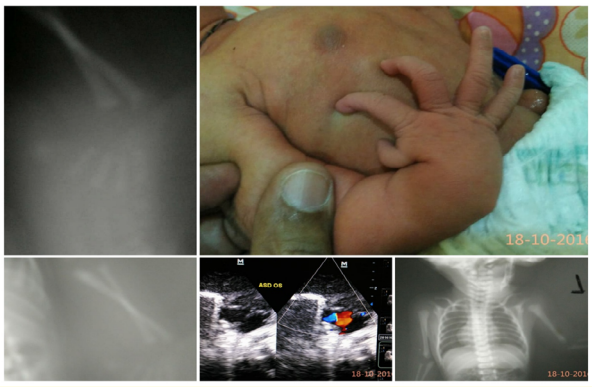

Figure 3: Upper row (from left to right) a) X ray right hand showing four metacarpals and rudimentary right thumb b) picture of right upper limb with right hand thumb hypoplasia. Lower row (from left to right) a) X ray of left forearm showing presence of both forearm bones b) Echo picture showing ASD ostium secundum c) X ray chest showing right atrial enlargement.

Literature Review

Synonyms:

1. Heart hand syndrome
2. Cardiolimb syndrome
3. Atriodigital syndrome
4. Holt Oram syndrome.

History: Holt. M and Oram. S were first to publish an article in the year 1960 on heart and hand defects in four generations within a family with the title "Familial heart disease with skeletal malformations" ([1], p: 236-40). All affected family members showed similar findings especially cardiac defects, ASD and thumb abnormalities. Similar findings were also reported by McKusick in the same year 1960 [2] with title term as "Atriodigital dysplasia". Similar findings with a single gene defect on chromosome 16 was reported in two family case series by Massumi. R.A. A and Netter D.O in the year 1966 (p: 73-75) [3].

Definition: It is an autosomal dominant syndrome involving anomalies of arm and hand bones with congenital cardiac defects. Commonly presents with hypoplasia or aplasia of thumbs and or radial bones of forearms and ASDs. Incidence is approximately 1 in 100000 live births ([4], p: 1-8).

Aetiology: The TBX5 gene is essential for heart and hand development and located on long arm of chromosome 12 ([5], p: 1739-1751). This gene produces TBOX5 protein which acts as a transcription factor (p: 1740). It involves in development of heart, septal formation, formation of conductive tissue of heart and development of hands during five to seven weeks of gestation ([6], p: 195-221). Mutations involving this gene on chromosome 12q2 locus results in Holt Oram syndrome with autosomal dominant inheritance ([7], p: 885-891). In majority of cases (85%) of HOS, new mutations occur [8]. The TBX5 gene mutation may cause atrial fibrillation and bicuspid aortic valve disease ([9], p: 1, 7).

Clinical features: Skeleton limb deformities is the common presenting feature. Hypoplasia or aplasia of preaxial digits especially thumbs along with underdeveloped or absent metacarpal and radial bones commonly found. Hypo plastic thumb may show triphalangism. This may result in delayed or absent pincer grasp which clearly noticeable when hand is supinated. Skeletal involvement may be bilateral or unilateral. In unilateral involvement, left upper

S. No.	Characters	Case 1	Case 2	Case 3
1.	Sex	Male	Male	Male
2.	Maternal age	23 years	21 years	22 years
3.	Consanguinity	Absent	2nd degree	Absent
4.	Family history	No similar history	No similar history	No similar history
5.	Mode of delivery	LSCS	LSCS	LSCS
6.	Clinical presentation	On day < 1, RD and upper limb defects	On day < 1, RD and upper limb defects	On day 2, Upper limb defects
7.	Skeletal deformities	Bilateral oligodactyly of hands with bilateral absence of thumbs and radial bones	Absence of left thumb, short forearm, hypo plastic left radius. Right thumb hypoplasia	Hypo plastic right thumb
8.	Cardiac defects	ASD -OS and OP, endocardial cushion defects, hsPDA, TR, PAH, relatively hypoplastic left heart without outflow tract obstruction.	ASD – OS, hsPDA, TR, PAH	ASD - OS
9.	Antenatal Anomaly scan	Done	Done	Done
10.	Duration of hospital stay	Five days and discharged on request	Seven days	Not admitted.
11.	Management	In patient NICU care	In patient NICU care	OPD management
12.	Referral	Orthopaedic and Paediatric Cardiology	Orthopaedic and Paediatric Cardiology	Orthopaedic and Paediatric Cardiology.

Table: Characteristic features of individual cases.

limb commonly affected ([10], p: 2637). Short ring fingers with fourth metacarpal dysplasia reported by Brockhoff CJ ([11], p: 1395). Uncommonly, other bones can also be involved like carpal bones, clavicles and scapulae. In most severe case, the whole upper limb may be rudimentary or phocomelia ([4], p: 1-3).

Majority of cases are associated with congenital cardiac defects. The ASD of ostium secundum (60.3%) is the most common cardiac defect ([12], p: 1996). Other possible cardiac defects include ASD of ostium primum, VSDs, cardiac conduction defects, brady-arrhythmias, fibrillations, wandering pacemaker and heart blocks ([10], p: 2636). In partial phenotypically presented cases, unrecognized ASDs may run in the families. Miller AB., *et al*. reported HOS with left thumb hypoplasia, ASD OS and mitral valve prolapse ([13], p: 231). Kumar V., *et al*. reported a case of HOS with tetralogy of Fallot ([14], p: 97).

Diagnosis: Diagnosis of Holt Oram Syndrome is made on the basis of physical examination findings and supportive evidence from typical skeletal x ray findings and detection of cardiac defects by echocardiogram. ECG shows conduction abnormalities of heart. Family members should be screened for cardiac defects especially ASDs with echocardiogram. In difficult cases, genetic testing should be ordered.

Management: After initial management of transitional maladaptation in NICU, further management includes 1. Orthopaedic consultation for the role of prosthetic implantation or tendon transfer surgery to improve functional ability for carrying out day to day activities. 2. Cardiac team consultation for corrective surgery of cardiac defects to improve quality and quantity of life. 3. Psychiatric consultation for the whole family to treat anxiety, depression and preparedness for unexpected medical condition in the neonate

and its consequences in the family. 4. Physiotherapy to improve strength of existing muscles and joint movements. 5. Financial management and medical insurance for medical expenses and long term follow up.

Discussion

All our three cases belonged to three different families and showed different phenotypical presentation with varying severity from the most severe case to mild case ([12], p: 1996). Among the three presented cases, case one is the most severe form with severe skeletal anomalies and cardiac defects ([15], p: 300-1). Baby had recurrent respiratory tract infections (RTIs) during infancy and needed hospitalization. Baby was planned for corrective cardiac surgery under state sponsored insurance (Arogyasri) policy but failed for anaesthesia fitness due to recurrent RTIs. Baby failed to thrive and expired in a referral centre due to severe RTI and cardiorespiratory failure. Case two is a moderate phenotypical expression with follow up by multidisciplinary team at a teaching hospital. Case three is a partial phenotypical expression and lost for follow up.

Unilateral skeletal deformities in Holt Oram syndrome are common on left side but in our case three, we found on right side ([10], p: 2636-7). Thumb defects and ASDs of OS variety were found in all three cases. All babies belonged to male sex and born to young couple with no such family history and may indicate new mutations. All pregnant women underwent antenatal anomaly scans but lost detection and potential antenatal counselling for couple and family ([16], p: 171).

Conclusion

1. In spite of advances in medical technology and training, skeletal hand defects and cardiac septal defects are missing antenatal detection. High index of suspicion, regular special training on early antenatal ultrasound anomaly scan for physicians utilizing 3D/4D USS technology may improve anomaly detection rate ([17], p: 651, 663).
2. Birth of a baby with congenital anomalies pose severe mental anguish among parents and family. Early antenatal detection of congenital anomalies and antenatal counselling give an opportunity for family to decide further on continuation of pregnancy ([16], p: 174).
3. State sponsored insurance policies are the only hope for families belonging to poor socioeconomic strata. They should be available at free of cost to all such babies for corrective surgeries, prosthesis implantation and long term follow up [18,19].

Conflict of Interest

There is no conflict of interest.

Sponsorship

There is no sponsorship for this study article.

Bibliography

1. Holt M and Oram S. “Familial Heart Disease with Skeletal Malformations”. *British Heart Journal* 22 (1960): 236.
2. McKusick VA. “Medical Genetics, 1960”. *Journal of Chronic Diseases* 14 (1960): 1.
3. Mussumi RA and Nutter DO. “The Syndrome of Familial Defects of Heart and Upper Extremities (Holt Oram Syndrome)”. *Circulation* (1966): 73-75.
4. National Organization for Rare Disorders (NORD), Holt Oram Syndrome 1-8; rare diseases.org-diseases/holt-oram syndrome (2020).
5. Horb ME and Thomsen GH. “Tbx5 is Essential for Heart Development, 126 (1999): 1739-17751.
6. Steimle JD and Moskowitz IP. “TBX5: A Key Regulator of Heart Development”. *Current Topics in Developmental Biology* 122 (2017): 195-221.
7. Bassen CT., *et al.* “The Clinical and Genetic Spectrum of Holt-Oram Syndrome 330.13 (1994): 885-891.
8. McDermott DA., *et al.* “Holt Oram Syndrome, Gene Reviews, Seattle (WA): University of Washington, Seattle (2004).
9. Jiang WF., *et al.* “A Novel TBX5 Mutation Predisposes to Familial Cardiac Septal Defects and Atrial Fibrillation as well as Bicuspid Aortic Valve”. *Genetics and Molecular Biology* 43.4 (2020):1-10.
10. Bohm MMD. “Holt-Oram Syndrome”. *Circulation* 98 (1998): 2636-2637.

11. Brockhoff CJ MD., *et al.* "Holt-Oram Syndrome". *Circulation* 99 (1999): 1395-1396.

12. Sletten LJ and Pierpont MEM. "Variation in Severity of Cardiac Disease in Holt-Oram Syndrome". *American Journal of Medical Genetics* 65 (1996): 128-132.

13. Miller AB., *et al.* "Prolapsed Mitral Valve Associated with the Holt-Oram Syndrome". *Chest* 67 (1975): 2.

14. Kumar V., *et al*. "Tetralogy of Fallot with Holt-Oram Syndrome". *Indian Heart Journal* 6401 (2012): 95-98.

15. Newbury-Ecob RA., *et al*. "Holt-Oram Syndrome: a clinical genetic study". *Journal of Medical Genetics* 33 (1996): 300-307.

16. Medjedovic E., *et al.* "Holt-Oram Syndrome: The Importance of Perinatal Detection". *Donald School Journal of Ultrasound in Obstetrics and Gynaecology 14*.2 (2020): 172-174.

17. Barisic LS., *et al.* "Diagnosis of Foetal Syndromes by Three- and Four-Dimensional Ultrasound: is there any improvement?" *The Journal of Perinatal Medicine* 45.6 (2007): 651-665.

18. Bassen CT., *et al.* "Different TBX5 interactions in Heart and Limb defined by Holt-Oram Syndrome Mutations". *Proceedings of the National Academy of Sciences of the United States of America* 96 (1999): 2919-2924.

19. Silverman ME., *et al.* "The Holt-Oram Syndrome: The long and short of it" 25.1 (1970): 11-17.