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Case Report

Holt-Oram Syndrome – A Case Report and a Short Review

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Abstract

Holt-Oram syndrome also known as the heart-hand syndrome type 1, is an autosomal dominant rare congenital disorder, manifested as a conglomeration of various skeletal and cardiac abnormalities. The list of differential diagnoses of such abnormalities is extensive but careful examination can point towards a specific diagnosis even without genetic testing in a resource-limited country. We present a sporadic case of Holt-Oram syndrome with OS-ASD highlighting the diagnostic problem without genetic testing and discussing differentiating salient features of most of the syndromic associations.

Keywords: holt-oram syndrome; atrial septal defect; asd; absent radius; case report

Introduction

Holt-Oram syndrome, a rare congenital disorder with a conglomeration of various defects especially skeletal and cardiac abnormalities, is an autosomal dominant disorder that was first described by Holt and Oram in 1960 in family members across four generations.[1] Differentiation of closely related phenotypic disorders is possible with good clinical examination even in the absence of genetic testing in a resource-limited country, as cardiac involvement is not the same for all. We present a case of Holt-Oram syndrome with cardiac involvement and a brief review of differentiating close mimickers **(Table 1)**.

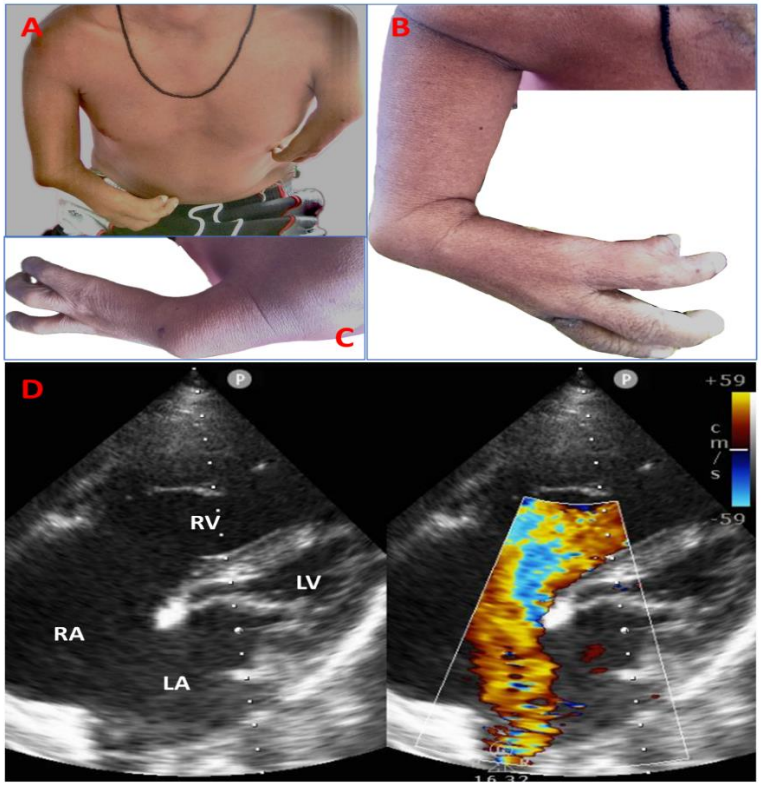
	Holt-Oram syndrome	Thrombocytopenia absent radius syndrome	Phocomelia	Ellis-van Creveld syndrome
Synonyms	Heart-hand syndrome	TAR syndrome	Thalidomide syndrome	Chondroectodermal dysplasia Mesoectodermal dysplasia
Incidence	1 in 100,000 (M=F)	0.5-1 in 100,000 (M=F)	0.62 in 100,000 (M=F)	0.5-1.6 in 100,000 (M=F)
Inheritance pattern	AD	AR	Undetermined > Thalidomide toxicity	AR
Gene	TBX5	RBM8A	-	EVC2
Chromosome	12q24.1	1q21.1	-	4p16.2
Classical skeletal involvement	Thumb (+/- or hypoplasia) Absent radius (+/- or hypoplasia)	Bilateral absence of the radii with the presence of both thumbs (100%) Lower limb defects (50%)	Absence or hypoplasia of arm/forearm with near normal hands/ feet One limb (56%) Two limbs (40%) UL>>LL Left>Right	Short-limb dwarfism Partial cleft lip Defect in alveolar ridge, Hypodontia Centrifugal shortening of limbs
Predominant cardiac involvement	OS-ASD > VSD Conduction abnormalities	OS-ASD > VSD >> TOF (17%)	Uncommon (TOF)	OP- ASD Single atrium
Mental retardation	-	-	-	++/-
Thrombocytopenia	-	+	-	-

		(usually <50,000 platelets/mL) 96%		
Cow's milk allergy	-	+	-	-
Gastrointestinal/ Genitourinary anomalies	+/-	+/- (~25%)	+/-	+/-

TAR - Thrombocytopenia absent radius; AD – autosomal dominant; AR – autosomal recessive; TBX5 – T-Box Transcription Factor 5; RBM8A - RNA-binding motif protein 8A; EVC2 - Ellis van Creveld syndrome 2; UL – upper limb; LL – lower limb; OS-ASD – ostium secundum atrial septal defect; VSD – ventricular septal defect; TOF – tetralogy of Fallot; OP-ASD – ostium primum atrial septal defect.

Case: A 45-year-old man presented with NYHA functional class II dyspnoea for 6 months and was referred. He denied any history of recurrent lower respiratory tract infection or cyanosis. There was no significant family history. Clinical examination revealed no facial dysmorphism, normal hairline, no chest cage abnormalities, and no significant dental or eye abnormalities. Upper limb examination showed asymmetric limb shortening (right > left), shorter humerus on the left side, absent radius bilaterally and short ulna bilaterally **(Figure 1A, B, C)**. There were symbrachydactyly and syndactyly. The thumb was absent bilaterally. Lower limbs were normal.

Cardiovascular examination was suggestive of pre-tricuspid septal defect with a significant left to right shunt. Other system examinations did not reveal any abnormalities. The electrocardiogram showed an incomplete right bundle branch block with a normal PR interval with an axis of -30 degrees. Chest X-ray showed increased pulmonary blood flow and mild cardiomegaly. The complete blood count was normal. The echocardiogram revealed normal left ventricular systolic function, dilated right ventricle, right ventricular systolic pressure of 45mmHg, and 30mm ostium secundum atrial septal defect (OS-ASD) with a left to right shunt **(Figure 1D)**. He is awaiting a device closure.



A, B, C: Clinical image of patient 1 showing asymmetric limb shortening (right > left), shorter arm and forearm on the left side. There is symbrachydactyly and syndactyly. There are four and three fingers on the right and the left side, respectively. The thumb is absent bilaterally; D. 2D echocardiogram in apical 4-chamber view showing large ostium secundum atrial septal defect with left to right shunt with dilated right atrium and ventricle.

Discussion

Holt-Oram syndrome also known as the heart-hand syndrome type 1, is an autosomal dominant disorder that is characterised by upper limb skeletal defects in conjunction with congenital heart lesions. This is caused by heterozygous mutation in the TBX5 gene (encoding T-box5 transcription

factor) on chromosome 12q24.1, which is responsible for cardiac septation and development of limbs. Nearly 58% of the clinically suspected Holt-Oram syndrome carry this mutation.[2] 60% of the cases are familial, the rest being sporadic.[3] It is reported to have 75% penetrance for cardiac defects. Wide phenotypic variability and de novo mutation make the prediction of malformation difficult.[4] The incidence of Holt-Oram syndrome is around 0.001% with no sexual predilection.

The classical manifestations are upper limb malformation, congenital heart malformation, and conduction system defects. Upper-limb skeletal abnormalities can be unilateral or bilateral (96%), symmetric or asymmetric (91%).[2] When unilateral, mostly it affects the left side. Fingerisation of the thumb or triphalangeal thumb is one of the characteristic features of this

syndrome. Absence or hypoplasia of thumb/ radius, fusion or underdeveloped carpal bones are the other manifestations.

Cardiac defects are seen in 75% of the patients, predominantly OS-ASD followed by ventricular septal defects and other rarely reported anomalies like a bicuspid aortic valve, left ventricular non-compaction, patent ductus arteriosus, coarctation of the aorta, pulmonary stenosis, left superior caval vein.[2,5,6] Vanlerberg et al reported 78 patients of TBX5 mutation, of which 91% had congenital heart defects, atrial septal defect constituting around 62% followed by ventricular septal defect (35%) and atrioventricular septal defect (5%).[2] Complex cyanotic congenital heart defects (1.3%) and conduction abnormalities were less common.[2] Multisystem involvement is seldom reported.[7] A large prospective study including 1653 patients with upper limb malformations (clinically diagnosed as Heart-hand syndrome) by Yin et al showed that 11 % had echocardiographic and 1% had electrocardiographic abnormalities, the commonest being the atrial septal defect (38%) followed by tricuspid regurgitation (37%), ventricular septal defect (6%).[8] Conduction abnormalities were present only in 2.5%.[8] Management is directed to specific malformations and genetic counselling is recommended in all patients with Holt-Oram syndrome. Two variants of Holt-Oram syndrome have been described in the literature.

Heart-hand syndrome type 2: It is described only in two families to date, characterized by upper limb malformations (hypoplastic deltoids, brachytelephalangy type D, mild shortening of the fourth and fifth metacarpals in some individuals, and cardiac arrhythmias.[9,10]

Heart-hand syndrome type 3: It is described in three members of a Spanish family to date, which is characterized by a cardiac conduction defect (sick sinus, bundle-branch block) and brachydactyly, affecting principally the middle phalanges in conjunction with an extra ossicle on the proximal phalanx of both index fingers.

Cardinal features of syndromes associated with upper limb skeletal deformity and cardiac defect have been depicted in **Table 2.**

	Synonyms	Gene/Locus	Inheritance pattern	Cardiac involvement	Radial defects	Characteristic manifestations
Holt-Oram syndrome[2,8]	Heart-hand syndrome	TBX5 12q24.1	AD	90%	100%	Thumb (+/- or hypoplasia) Absent radius (+/- or hypoplasia)
Thrombocytopenia absent radius syndrome[11]	TAR syndrome	RBM8A 1q21.1	AR	15-30%	100%	Bilateral absence of the radii with the presence of both thumbs (100%) Lower limb defects (50%) Thrombocytopenia (96%)
Phocomelia[12]	Thalidomide syndrome	-	Sporadic	-	100%	Absence or hypoplasia of arm/forearm with near normal hands/ feet One limb (56%) Two limbs (40%) UL>>LL Left>Right
Ellis-van Creveld syndrome[13,14]	Chondroectodermal dysplasia Mesoectodermal dysplasia	EVC 2 4p16.2	AR	50-60%	93%	Short-limb dwarfism Partial cleft lip Defect in the alveolar ridge, Hypodontia Centrifugal shortening of limbs
Okihiro syndrome[15]	Duane syndrome Acro-renal-ocular syndrome (AROS) Duane-radial ray syndrome (DRRS)	SALL4 20q13.2	AD	23%	80%	Upper limb anomalies, ocular anomalies, renal anomalies
Fanconi pancytopenia[16]	-	Fanconi anaemia core complex gene	AR, XL	6%	35%	Pancytopenia, growth retardation, microcephaly
VACTERL association[17]	-	-	Sporadic	40-80%	40-50%	Vertebral defects, anal atresia/ stenosis, cardiac defects, tracheoesophageal fistula, renal anomaly, limb defects
Townes-Brockes syndrome[18]	-	SALL1 16q12.1	AD	9-40%	50-90%	Anal atresia, ears malformations, sensorineural deafness, triphalangeal thumbs, renal anomaly
Nager syndrome[19]	Acrofacial dysostoses 1 Split hand deformity - mandibulofacial dysostosis	SF3B4 1q21.2	AD	15%	100%	Mandibulofacial dysostosis, deafness, absent radii/ thumbs
Roberts syndrome[20]	-	ESCO2 8p21.1	AR	26%	100%	Growth retardation, craniofacial anomaly, limb reduction defects
Valproate embryopathy[21]	-	-	Sporadic	14-26%	30%	Neural tube defects, vertebral anomaly, cleft palate

TBX5 – T-Box Transcription Factor 5; RBM8A - RNA-binding motif protein 8A; EVC2 - Ellis van Creveld syndrome 2; SALL4 - Spalt Like Transcription Factor 4; SF3B4 - splicing factor 3b subunit 4; ESCO2 - establishment of sister chromatid cohesion N-acetyltransferase 2; TAR - Thrombocytopenia absent radius; AD – autosomal dominant; AR – autosomal recessive; XL – X-linked; UL – upper limb; LL – lower limb

Table 2: Cardinal features of syndromes associated with upper limb skeletal deformity and cardiac defect

Conclusion

Skeletal deformities and cardiac malformations often go hand-in-hand. Proper clinical evaluation may indicate a specific syndrome that can predict cardiac involvement in syndromic patients. We present a sporadic case of Holt-Oram syndrome with OS-ASD highlighting the diagnostic problem in the absence of genetic testing.

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Abbreviation: None

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