

Holt-Oram Syndrome: A Rare Variant

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Abstract

Holt-Oram syndrome is an autosomal dominant disorder, characterised by skeletal abnormalities of the upper limb associated with congenital heart defect, mainly atrial and ventricular septal defects. Skeletal defects exclusively affect the upper limbs in the preaxial radial ray distribution and are bilateral and asymmetrical. They range from clinodactyly, absent or digitalised thumb, hypoplastic or absent radii, and first metacarpal to hypoplastic ulna and carpal bone anomalies. Cardiac involvement ranges from asymptomatic conduction disturbances to multiple structural defects. Structural defects are seen in 75% of the cases and include both atrial and ventricular septal defect. More complex cardiac lesions such as Tetralogy of Fallot, endocardial cushion defects, double outlet right ventricle, and total anomalous pulmonary venous return are observed uncommonly. An aneurysm of the interatrium septum is an infrequent finding in infants. It has been speculated that atrial septal aneurysm (ASA) is a direct source of thrombus formation. Paradoxical embolism of venous thrombi across a right to left shunt is possibly responsible for the cryptogenic stroke in a patient with ASA. However, coagulopathy associated with cyanotic congenital heart defect may also be contributory. Our patient had a rare association of complex cardiac lesion (tricuspid atresia, pulmonary stenosis, atrial septal aneurysm) with cardiac conductive defects and left parietal infarct along with the usual skeletal abnormalities.

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Keywords • Holt-Oram syndrome • Congenital heart disease
• Tricuspid atresia

What's Known

- Holt-Oram syndrome is characterized by skeletal abnormalities in the upper limbs and is associated with congenital heart defects, mainly atrial and ventricular septal defects. A few cases have been reported with tricuspid atresia or with atrial septal aneurysm.

What's New

- To our knowledge, none of the cases published in the literature have reported tricuspid atresia, atrial septal aneurysm, and pulmonary stenosis in a single patient.

Introduction

Holt-Oram syndrome is an autosomal dominant disorder associated with aplasia or hypoplasia of the digital rays and radius with CHD. It was first reported in 1960 by Mary Clayton Holt and Samuel Oram. With equal sex distribution, 1 out of 100,000 live births is affected. Seventy-five percent of individuals have CHD, with ostium secundum atrial septal defect (60%) being the most common followed by ventricular septal defect. Even if a congenital heart malformation is not present, 39% of the individuals with this syndrome may have cardiac conductive defects.¹ Complex cardiac lesions associated with HOS are being increasingly reported and constitute 18% of the cardiac defects.²

ASA is uncommon and hitherto unreported finding in the paediatric age group and in patients with HOS. It has been speculated as a direct source of thrombus formation and cryptogenic stroke.

We are reporting a rare variant of this syndrome having a complex congenital cardiac disease, including tricuspid atresia, pulmonary stenosis, and atrial septal aneurysm in association with the usual ASD, VSD, and the structural skeletal defects along with an unusual presentation of stroke.

Case Presentation

A 4-month-old male child born out of a non-consanguineous marriage presented with a history of cyanosis since three months of age and failure to thrive. The mother noticed cyanotic spells, two to three episodes in a day since the last month. There was no history of recurrent chest infections. Antenatal history was uneventful with no history of drug intake or radiation exposure to the mother; however, she had a bad obstetric history (three miscarriages). There was no history of skeletal abnormalities in the family.

On musculoskeletal examination, both forearms were short, malformed, and associated with flexion deformity at the elbow along with wrist joints. Similarly, both hands were malformed, laterally rotated, abducted, and parallel to the upper arm with bilateral absence of thenar fold (figure 1A). The thumb was rudimentary in the left and absent on the right side with clinodactyly. A prominent dimple was present on the ulnar aspect of the wrist. No obvious skeletal deformities were observed in the lower limbs or elsewhere.

Physical examination revealed central cyanosis. The heart rate was 110 beats/min, respiratory rate 40/min, blood pressure 90/54 mmHg and systemic oxygen saturation was 55% in room air. His weight, length, and head circumference were 4kg (<3 SD), 61 cm (<3 SD), and 38 cm (<3 SD), respectively.

Cardiovascular examination revealed an ejection systolic murmur grade III/VI at the left upper parasternal area. Examinations of other systems were normal. Haemogram, renal, and hepatic functions were normal. Arterial blood gas showed a PaO₂ of 24 mmHg and SPO₂ 48%.

Radiograph of upper limbs revealed a bilateral absence of radius and first metacarpal with an underdeveloped ulna (figure 1B) while that of chest reflected oligemic lung fields. Electrocardiogram manifested sinus rhythm, normal PR interval, P-pulmonale, left superior axis with slurring of QRS in lead III and aVL. Echocardiography (figure 2) showed a 3 mm ostium secundum atrial septal defect and a fenestrated atrial septal aneurysm with its excursion towards the left atrium (12 mm) with a right to left shunt. Tricuspid valve atresia, valvular pulmonary stenosis (55 mmHg) and inlet ventricular septal defect (1.03 cm) were also present along with normally related great arteries. Ultrasound abdomen and brain were normal. BT shunt was advised with the plan for future Fontan surgery and the patient was discharged.

The patient was readmitted after 10 days with complaints of abnormal movement of the right hand with loss of consciousness. On examination, the baby was afebrile with no neurodeficit and meningeal signs. The patient was started on intravenous fluid, antibiotic, anticonvulsant, and supportive care. Haemogram, blood pressure, and fundus were normal. Septic profile, serum electrolytes, and random blood sugar were normal. CECT brain showed subacute infarct in the left parietal region, which was confirmed by MRI. Coagulation profile was reported as normal. Doppler study of lower extremities excluded deep vein thrombosis. The patient was started on LMW heparin and discharged on warfarin and anticonvulsants. However, the patient had a seizure post tenth day of discharge, aspirated, and readmitted but could not be resuscitated and died.

Discussion

CHD and skeletal abnormality of upper limb together constitute heart-hand syndrome of which three subtypes are described. The heart-hand syndrome type I, also known as Holt-Oram syndrome is the most common and is usually associated with an atrial septal defect.³

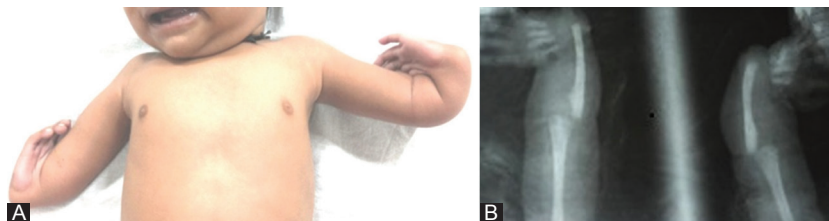


Figure 1: (A) The patient showing short forearm and flexion deformity at the wrist. Both hands are malformed, laterally rotated, and parallel to the upper arm with bilateral absence of thenar fold. (B) Plain radiograph of bilateral upper limbs showing absent radii, short and hypoplastic ulna, and absent first metacarpal.

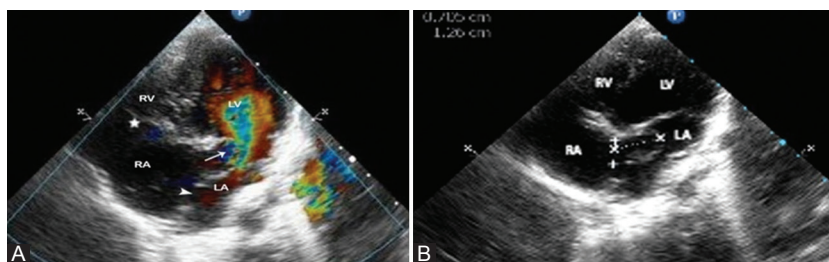


Figure 2: (A) 2D Doppler echo apical four-chamber demonstrating tricuspid atresia. *Atrial septal aneurysm with fenestration (arrow), atrial septal defect (arrowhead). (B) 2D echo apical four-chamber view demonstrating atrial septal defect and atrial septal aneurysm with excursion of 12 mm. RA: Dilated right atrium; RV: Small right ventricle; LA: Left atrium; LV: Left ventricle.

Holt-Oram syndrome is an autosomal dominant disorder with complete penetrance. Sporadic cases (up to 40%) represent new gene mutations. The underlying genetic defect is ascribed to the long arm of chromosome 12 (12q24.1). Although the diagnosis is essentially clinical, it can be confirmed through molecular genetic testing. About 70% of the patients who meet the clinical diagnostic criteria have a mutation in *TBX5* genes, which is associated with cardiac and skeletal development.⁴ Approximately 75% of patients have an underlying cardiac abnormality most commonly atrial or ventricular septal defect. Complex CHD may be present in up to 18% of patients which include mitral valve prolapse, hypoplastic left heart syndrome, endocardial cushion defect, coarctation of aorta, patent ductus arteriosus, pulmonary hypertension, Tetralogy of Fallot,⁵ double outlet right ventricle,⁶ truncus arteriosus, and total anomalous pulmonary venous return. The association with tricuspid atresia as in our case has been rarely reported.

Atrial septal aneurysm (ASA) is a localized saccular deformity of the interatrial septum, generally at the level of fossa ovalis that bulges into the right or left atrium or both with a reported prevalence 0.9% to 1.7% in children. Diagnostic criteria for atrial septal aneurysm include a sacculation in the interatrial septum with an excursion of 10 mm into the right or left atrium or the sum of bilateral excursions >10 mm.⁷ Alexander Olivares classified it into various subtypes depending upon the excursion of the atrial septal deformity into either atria or both (table 1). The presence of atrial septal aneurysm tends to aggravate stasis of left atrial blood flow and predisposes to systemic thromboembolism. Our case had type 2L atrial septal aneurysm and the brain CT-scan demonstrated ischemic infarcts that possibly reflected paradoxical embolism of venous thrombi across a right to left shunt through ASD or thrombus formation on the left atrial side of the aneurysm, which is supposed to be the more acceptable underlying mechanism.

Table 1: Alexander Olivares classifications of atrial septal aneurysm

Type 1R	The ASA protrudes from the midline of the atrial septum to the right atrium
Type 2L	The ASA protrudes from the midline of the atrial septum to the left atrium
Type 3RL	The maximal excursion of the ASA is toward the right atrium with a lesser excursion toward the left atrium
Type 4LR	The maximal excursion of the ASA is toward the left atrium with a lesser excursion toward the right atrium
Type 5	The ASA movement is bidirectional and equidistant to the right as well as to the left atrium during the cardiorespiratory cycle

In patients with cyanotic heart disease, underlying coagulopathy and polycythemia are responsible for predisposing them to stroke. However, in the index case, the presence of ASA may be an additional possible risk factor for ischemic stroke. Treatment for the prevention of recurrent stroke in patients with atrial septal aneurysm includes medical therapy with antiplatelet agents or anticoagulants. Surgical or percutaneous closure of the defects is the other option. Till date, there is not much literature available in the paediatric age group on ASA and stroke as well as its association with HOS.⁸

Individuals are at risk for cardiac conduction disease mainly sinus bradycardia, first-degree atrioventricular block, and right bundle branch block. In the index case, we noted intraventricular conduction defect manifesting as slurring of QRS in chest leads III and aVL.

Our case had type 2L ASA aneurysm with ischemic cerebral infarcts that possibly could have been due to minute LA clots with atrial septal aneurysm. This is the first reported case of Holt-Oram syndrome association with tricuspid atresia and atrial septal aneurysm. Skeletal malformations are characteristically limited to the upper limbs in the preaxial radial ray distribution. They include absent or digitalised thumb, clinodactyly, hypoplastic or absent radii and first metacarpal, hypoplastic ulna and carpal bone anomalies. Uncommon

subtypes of heart-hand syndrome are Tobatznik syndrome (type II) and Spanish variant (type III). Type II variant is associated with arrhythmia and type D brachydactyly, bifid thumbs, bowing of the radius, short arms, scoliosis, and facial dysmorphism. Cardiac conduction disorder and type C brachydactyly is characteristic of Spanish variant (type III). Differential diagnosis of these skeletal abnormalities includes thrombocytopenia absent radius syndrome, Roberts syndrome, thalidomide embryopathy, Fanconi anaemia and Edward syndrome.

Our case had the characteristic skeletal abnormalities of the upper limb, a normal platelet count, no history of skeletal deformity in the family and no history of radiation exposure and thalidomide intake in mother, thereby suggestive of the sporadic type of Holt-Oram syndrome.

Conclusion

Holt-Oram syndrome is known to be associated with a panorama of cardiac defects. Our case had a rare association of tricuspid atresia and atrial septal aneurysm (type 2L) along with pulmonary stenosis. In the presence of stroke in a patient with cyanotic CHD, echocardiography should include meticulous examination of atrial septum to exclude ASA.

Conflict of Interest: None declared.

References

1. Newbury-Ecob RA, Leanage R, Raeburn JA, Young ID. Holt-Oram syndrome: a clinical genetic study. *J Med Genet.* 1996;33:300-7. doi: 10.1136/jmg.33.4.300. PubMed PMID: 8730285; PubMed Central PMCID: PMC1050579.
2. Sletten LJ, Pierpont ME. Variation in severity of cardiac disease in Holt-Oram syndrome. *Am J Med Genet.* 1996;65:128-32. doi: 10.1002/(SICI)1096-8628(19961016)65:2<128:AID-AJMG9>3.0.CO;2-O. PubMed PMID: 8911604.
3. Holt M, Oram S. Familial heart disease with skeletal malformations. *Br Heart J.* 1960;22:236-42. doi: 10.1136/hrt.22.2.236. PubMed PMID: 14402857; PubMed Central PMCID: PMC1017650.
4. Debeer P, Race V, Gewillig M, Devriendt K, Frijns JP. Novel TBX5 mutations in patients with Holt-Oram syndrome. *Clin Orthop Relat Res.* 2007;462:20-6. doi: 10.1097/BLO.0b013e3181123ffe. PubMed PMID: 17534187.
5. Tidake A, Gangurde P, Shaikh Z, Mahajan A. Tetralogy of Fallot with Holt-Oram syndrome: case report and review. *Clin Res Cardiol.* 2015;104:790-3. doi: 10.1007/s00392-015-0858-8. PubMed PMID: 25903110.
6. Singh B, Kariyappa M, Vijayalakshmi IB, Nanjappa MC. Holt-Oram syndrome associated with double outlet right ventricle: A rare association. *Ann Pediatr Cardiol.* 2013;6:90-2. doi: 10.4103/0974-2069.107245. PubMed PMID: 23626447; PubMed Central PMCID: PMC3634259.
7. Silver MD, Dorsey JS. Aneurysms of the septum primum in adults. *Arch Pathol Lab Med.* 1978;102:62-5. PubMed PMID: 579965.
8. Razaq M, Parihar RK, Saini G. Atrial septal aneurysm and stroke. *Ann Pediatr Cardiol.* 2012;5:98-9. doi: 10.4103/0974-2069.93726. PubMed PMID: 22529616; PubMed Central PMCID: PMC3327030.