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Holt-Oram Syndrome; A Case report

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Abstract
Holt-Oram syndrome is a rare genetic autosomal dominant disorder which affects the preaxial radial ray of the upper limbs and septation of the heart and/or cardiac conduction. The present article describes the clinical and radiological features of Holt–Oram syndrome in a Tanzanian patient. This case emphasizes the importance of proper prenatal screening for congenital anomalies and the counselling of the parents.
Keywords: *Holt-Oram syndrome, Heart-hand syndrome, Ventricular Septal defect, TBX5 gene*

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Introduction

Heart-hand syndrome is a heterogeneous group of congenital malformations characterized by congenital heart defects and limb malformations. Holt- Oram syndrome (OMIM #142900) is the most common among the six Heart–hand syndromes (Welbeck *et al*., 1992) (Table 1). This syndrome was described in 1960 by Dr Mary Holt and Dr Samuel Oram. It is an autosomal dominant condition resulting from a mutation in *TBX5* located on chromosome 12q24.1, which regulates cardiac and limb morphogenesis (Terrett *et al*., 1994). It causes anomalies in the bony segment of the upper limbs and the cardiovascular system. The diagnosis is confirmed by *TBX5* gene analysis. However, sporadic mutations are common, and 26% of cases show no *TBX5* mutation (Newbury- Ecob *et al*., 1996). Our patient had bilateral radial ray limb deformities along with a congenital cardiac septal defect.

Table 1: Types of Heart-hand syndromes and associated features

Types	Syndromes	Features
1	Heart-hand syndrome type 1 (Holt-Oram Syndrome)	Defects in the preaxial radial ray of the upper limb bones and septation defects of the heart and/or cardiac conduction disease.
2	Heart-hand syndrome type 2 (Berk–Tabatznik syndrome)	Short stature, congenital optic atrophy and brachytelephalangy.
3	Heart-hand syndrome type 3, Spanish type	Cardiac conduction defect and brachydactyly affect principally the middle phalanges.
4	Heart-hand syndrome, Slovenian type	Brachydactyly with mild hand involvement and more severe foot involvement.
5	Brachydactyly-long thumb syndrome	Symmetric brachydactyly with long thumbs
6	Patent ductus arteriosus-bicuspid aortic valve syndrome	Hand anomalies include metacarpal hypoplasia

Case report

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The mother was delivered by c-section due to the previous scar at 41 weeks of GA at our hospital. The baby was born weighing 2.3 kg, and the APGAR score was 7 and 9 in the 1st and 5th minute, respectively. Her estimated gestational age was 40 weeks by using the Finstrom scoring technique indicating small for gestational age. The baby was able to breastfeed without any difficulties and passed both urine and meconium within 4 hours of birth.

Apart from polyhydramnios and features of intrauterine growth restriction (IUGR), the mother's antenatal period was uneventful. However, the underlying cause of polyhydramnios and IUGR could not be established. There was no history of consanguinity, teratogenic drug intake, radiation exposure, and no history of any apparent skeletal or heart abnormalities in the family of either the mother or father. The previous two siblings are healthy and developing normally. Ultrasound conducted during the second trimester (17th week) only showed polyhydramnios with no visible defects. On general examination, she looked stable with normal vitals. Occipital head circumference was 35.5 cm and a length of 49 cm.

On musculoskeletal examination (Figures 1-4) she had bilateral shortening of forearms and radial flexion deformity. She had a hypoplastic left thumb and an absent right thumb. Humerus was palpated on both upper arms. The lower limbs showed no apparent defects (Figure 4).

On central nervous system examination apart from the Moro reflex, the sucking and rooting reflexes were normal. No spina bifida swelling on inspection. On cardiovascular system examination, S1 and S2 were heard with no audible murmur. Other systemic examinations were unremarkable.

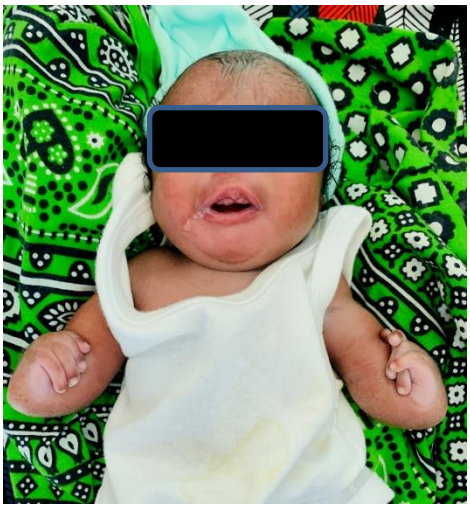

Figure 1: upper limbs deformity

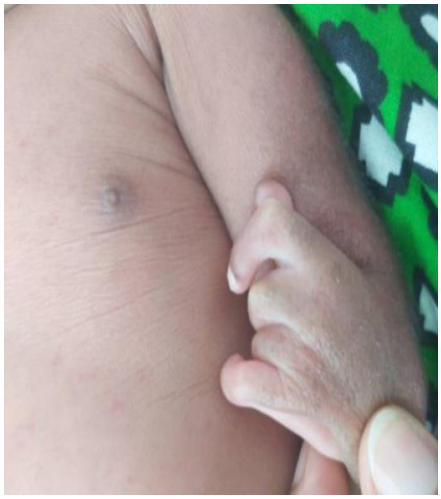

Figure 2: hypoplastic left thumb

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Figure 3: Absence of the right thumb


Figure 4: normal lower limbs

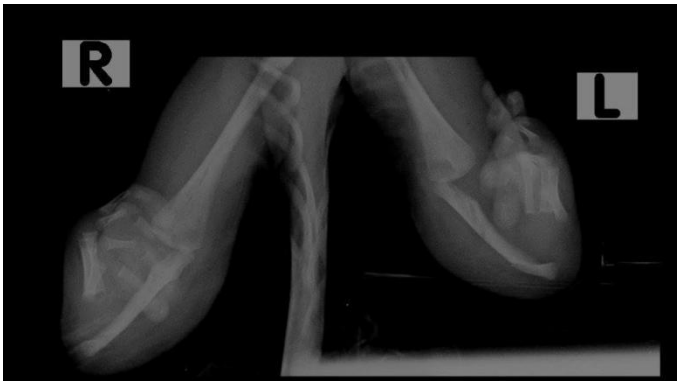

Figure 5: X-ray of right (R) and left (L) upper limb, showing absent radius bilaterally

X-ray workup of both upper limbs showed an absent radius bilaterally (Figure 5). Echocardiography showed medium-sized membranous VSD. ECG could not be conducted. Parents were counselled regarding the condition of the baby.

On her second day of life, she died in her sleep. The cause of death was suspected to be sudden infant death syndrome, probably due to aspiration or heart conduction abnormality. Genetic testing could not be done due to financial constraints.

Discussion

Our case meets the strict Holt-Oram syndrome clinical criteria of McDermott et al, i.e. preaxial radial ray upper limb abnormalities and septation defect of the heart without a lower limb, postaxial upper limb, craniofacial, pulmonary, genitourinary, and gastrointestinal malformations (McDermott *et al.*, 2005). Holt-Oram syndrome is the most common of the heart-hand syndromes. It is characterized by congenital cardiac defects and malformation of the upper limbs (Basson *et al.*, 1994).

It occurs in 1:100,000 individuals among Americans but its incidence among Africans is unknown. *TBX5* is a T-box containing transcription factors involved in forearm and heart development. Though autosomal dominant, about 85% of cases may be due to sporadic mutation, as was observed in this case because no other family member had similar defects (Terrett *et al.*, 1994).

Upper limb abnormalities are always present, and the presence of lower limb abnormalities excludes the diagnosis because the mutant gene affects the embryogenesis during the 4th and 5th week of intrauterine life when the lower limbs are not differentiated (Wall *et al*., 2015). The characteristic malformation in the upper limb is the absent, underdeveloped, or triphalangeal thumb. There are malformations of the metacarpals, hypoplastic or absent radii or humerus. Malformations can be symmetric or asymmetric and unilateral or bilateral (Holt *et al*., 1960).

The various cardiac defects associated with Holt–Oram syndrome are ASDs, VSDs, PDAs, endocardial cushion defects, hypoplasia of the left ventricle, and pulmonary stenosis (Holt *et al*., 1960). Conduction disturbances are sometimes associated with Holt–Oram syndromes such as first-degree AV block, sinus bradycardia, wandering pacemaker, and atrial fibrillation (Cerbai *et al*., 2008). The morbidity and mortality depend on the severity of cardiac defects and the stage of their diagnosis.

The main aim of management includes physical therapy to at least provide some function to the deformed upper limbs and primarily the detection of cardiac abnormalities so that they can be corrected at an early stage to prolong the longevity of patients (Wall *et al*., 2015).

Conclusion

The Holt–Oram syndrome is a rare disorder with a constellation of preaxial radial ray upper-limb deformities and cardiac septation defects. Diagnosis is based on careful physical examination, imaging and family history. Molecular genetics though not available at all places, can be used for confirmation of the disease. Treatment depends on the management of specific symptoms. This article aimed to present the classic findings in a Tanzanian neonate born with defects in the upper limb and septation of the heart. This report also highlights the diagnostic and management challenge of an uncommon Heart–hand syndrome by clinicians in a low-resource setting.

Acknowledgement

Regency Management approved the case follow up upon consent from the parents
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Conflict of interest

The authors declare no conflict of interest.

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