CASE REPORT

https://doi.org/10.3126/njms.v9i2.72348

Thrombocytopenia in Newborn with Holt-Oram Syndrome: A Rare Case Report

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Received: February 16, 2024 **Accepted: June 5, 2024** **Published: July 31, 2024**

Cite this paper: Sah M, Shah RK, Gauchan E. Thrombocytopenia in Newborn with Holt-Oram Syndrome: A Rare Case Report. Nepal Journal of Medical Sciences,2024;9(2):18:79-84 https://doi.org/10.3126/njms.v9i2.72348

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ABSTRACT

Holt-Oram syndrome or heart-hand syndrome is a rare congenital disorder characterized by a combination of upper limb abnormalities and congenital heart lesions. We report a case of a neonate with congenital anomalies of the left upper limb (radial club hand, absent radius bone, and absent thumb) with multiple cardiac defects (atrial septal defect, ventricular septal defect, and patent ductus arteriosus). This case report emphasizes the need for screening of cardiac anomalies in all newborns with upper limb deformities.

Keywords*: Heart-hand Syndrome, Holt-Oram Syndrome, Newborn.*

INTRODUCTION

Holt-Oram syndrome, also known as the heart-hand syndrome, is a rare congenital disorder characterized by upper limb abnormalities in association with congenital heart lesions.[1] Holt and Oram reported it for the first time in a family with congenital thumb anomalies and atrial septal defects in 1960.[1, 2] It has an incidence of 1 in 100,000 live births, with almost 95% of cases having congenital heart disease.[3] About 70% of cases carry a mutation in TBX5 gene. [4] Majority of the cases (60%) are familial.[5] Involvement of the upper limb is seen in all cases but with variable presentation. Upper limb malformations can involve abnormalities in the radial bone or carpal bones. These defects may occur unilaterally or bilaterally and can present symmetrically or asymmetrically.[6] Cardiac defect is present in 75% cases and commonly presenting as ostium secundum ASD (atrial septal defect) and VSD (ventricular septal defect).[7] Although several cases have been reported in newborns elsewhere, this is the first case being reported from Nepal.

CASE

A term intrauterine growth restricted (IUGR) male neonate with a birth weight of 1550 gram (<10^{th} percentile) was delivered via emergency LSCS for uteroplacental insufficiency at 39^{+6} weeks of gestation to a 34-year-old multigravida with an uneventful antenatal history, non-consanguineous marriage, no family history of limb deformity or cardiac defects. The baby required resuscitation at the time of birth due to poor respiratory effort and heart rate less than 60 beats/min. Apgar scores at 1, 5, 10

and 15 minutes of life were 4, 4, 6 and 7 respectively.

Examination showed radial clubbing of bilateral hands and absence of thumb on the left side. Bilateral lower limbs were normal (Figure 1). No other gross anomalies were noted in the head-to-toe examination. Head circumference and length were 28 cm (<10th percentile) and 40 cm (<10th percentile) respectively at birth. On systemic examination, parasternal murmur was present at left lower sternal border.

His radiograph revealed an absent radius and thumb on the left side, while the right upper limb was normal (Figure 2). Complete blood count showed thrombocytopenia with platelet count of 110,000/mm^3. Renal function tests, liver function test, serum calcium and C-reactive protein were within normal limits. Neurosonogram, Ultrasonography (USG) of abdomen and X-ray of Kidney, Ureter and Bladder (KUB) were normal. On two-dimensional echocardiography, perimembranous ventricular septal defect (VSD) of 3.5 mm with left to right shunt, small patent foramen ovalis without significant shunt, and patent ductus arteriosus (PDA) of 2.9 mm were found.

A clinical diagnosis of Holt Oram Syndrome was made based on the patient's congenital cardiac defects and forelimb deformities.

The neonate was admitted in Neonatal Intensive Care Unit (NICU) for five days during which he received oxygen therapy, intravenous antibiotics and intravenous fluid. Genetic analysis could not be done due to the patient's financial constraints and non-availability in our institute. He was discharged against medical advice on his family's request and was lost to follow up.

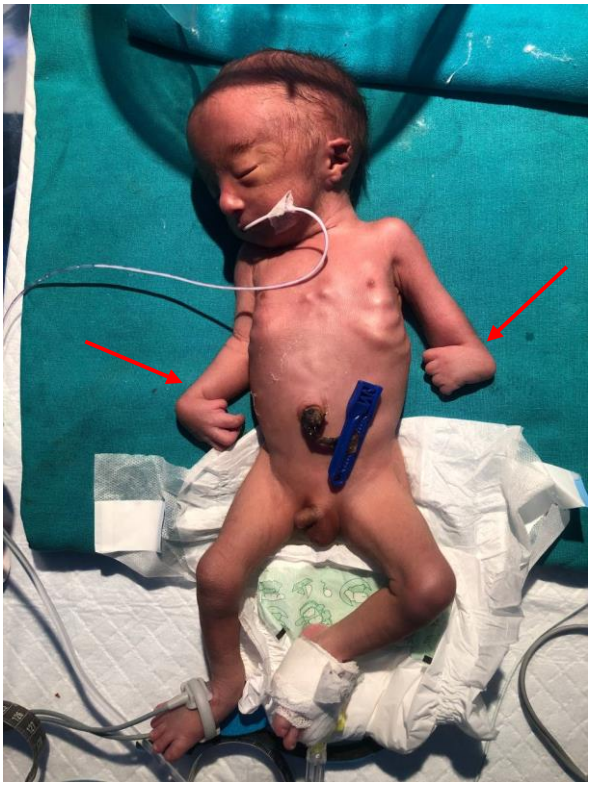

Figure 1: Neonate with bilateral radial clubbing of hand and absent left thumb

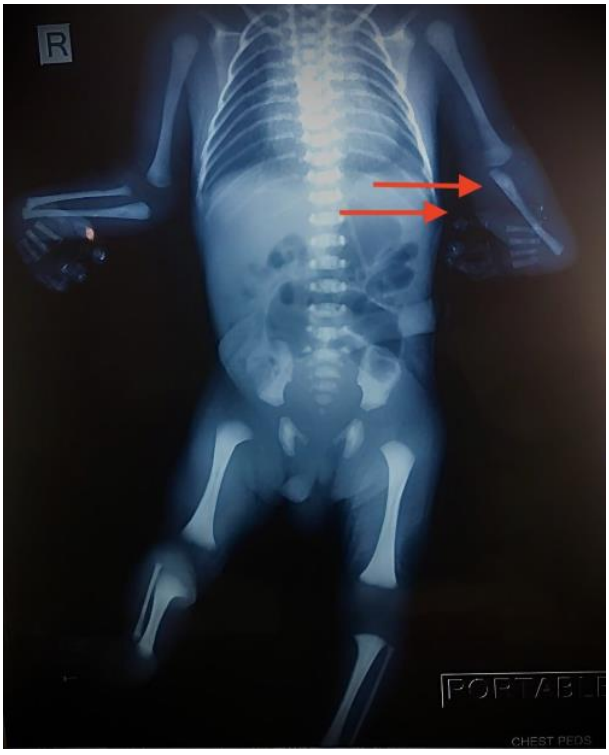

Figure 2: Xray showing absent left radius and left thumb

DISCUSSION

Holt-Oram Syndrome, known by other names such as Heart-Hand Syndrome or AtrioDigital Dysplasia, is an autosomal dominant disorder. This condition is associated with the TBX5 gene found on chromosome 12 (12q24.1), which accounts for approximately 70% of the most prevalent mutations seen in clinical diagnoses.[4]

Variants in the TBX5 gene were first identified as the cause of Holt-Oram syndrome (HOS) in 1997. The gene encodes a transcription factor in the T-box family, which is critical for regulating diverse developmental processes in vertebrates.[8] During heart development, TBX5 is initially expressed uniformly but later becomes restricted to the left side as the heart tube loops, with no expression observed in the right ventricle. This selective expression is essential for cardiomyocyte proliferation, differentiation, septum formation, and the development of the conduction system.[9] In limb development, TBX5 expression is specific to forelimbs and absent in hindlimbs. It plays a key role in initiating the epithelio-mesenchymal interaction between FGF10 in mesenchymal tissues and FGF8 in the apical ectodermal ridge during early limb growth. In later stages, TBX5 is involved in the patterning of muscles and tendons but is no longer required for further limb outgrowth. [8]

Familial transmission accounts for majority of cases while 40 to 85% of cases are sporadic resulting from new mutations.[5] While autosomal dominant Holt-Oram syndrome (HOS) typically exhibits almost full penetrance and variable expression, subtle limb issues may remain inconspicuous from a clinical perspective unless radiographic studies are conducted. [7, 10]

The clinical manifestations of HOS can vary greatly, even in individuals from the same family, despite sharing the same genetic mutation. This variability includes differences in the severity of heart defects and limb malformations. Genetic testing plays a crucial role in diagnosing HOS, particularly when the clinical symptoms are mild or when there is variability in expression among family members. Identifying mutations in the TBX5 gene allows for accurate diagnosis, informs clinical management, and provides insights into disease prognosis. Genetic testing also helps assess recurrence risks for other family members and enables prenatal screening when a known familial mutation exists.[11]

Given the absence of any prior instances of a similar illness in the family's medical history and the lack of observable limb deformities in the parents, the initial case could be considered sporadic.

Upper limb deformities in Holt-Oram syndrome (HOS) are typically bilateral but often exhibit asymmetry, as seen in this case. Occasionally, only one upper limb is affected. The range of limb defects varies from mild, such as slight abnormalities in carpal bones, to severe, including phocomelia. Frequently, there is either a partial or complete absence of the radius bone in one of the forearms. However, abnormalities in the ulnar bone tend to suggest other diagnoses. The thumb can present as triphalangeal (finger-like), hypoplastic, or, as in the reported case, completely absent.[2]

Cardiac abnormalities are present in about 75% of patients (95% in familial cases). These cardiac abnormalities can occur individually or as complex heart defects. The most commonly observed cardiac anomalies include ostium secundum atrial septal defect (ASD) and

ventricular septal defect (VSD).[7,12] Conduction defects, such as atrioventricular block and right bundle branch block, as well as arrhythmias like atrial flutter, fibrillation, supraventricular tachycardias (SVT), and Wolf Parkinson White (WPW) syndrome, may also be present.[9]

Thrombocytopenia was observed with a platelet count of 110,000/mm3 in this case. This finding was unique as we found no case of Holt-Oram Syndrome with reduced platelet count in the literature. One of the possible reasons for this can be due to uteroplacental insufficiency. However, there was no definitive way to establish that the thrombocytopenia was due to uteroplacental insufficiency, or it coexisted with Holt-Oram Syndrome.

Thrombocytopenia-Absent Radius (TAR) syndrome, an autosomal recessive condition can present with similar clinical features and needs to be considered as a differential diagnosis. TAR syndrome is characterized by the absence of radial bones in both limbs with presence of both thumbs and low platelet counts. In TAR syndrome, cardiac issues are present in approximately 33% of cases.[13] In this case study, the possibility of TAR syndrome as a diagnosis was taken into account, primarily due to the absence of any phenotypic abnormalities in the parents. This lack of phenotypic abnormalities suggested a higher likelihood of an autosomal recessive condition, similar to TAR syndrome. Despite the presence of thrombocytopenia, absence of the left thumb significantly reduced the likelihood of TAR syndrome as a diagnosis, as thumbs are consistently present in individuals with TAR syndrome.

Fanconi anemia was excluded as a diagnosis since the neonate did not exhibit symptoms of pancytopenia, such as petechiae, bruising, or pallor, and laboratory results confirmed the absence of pancytopenia.[14]

VACTERL association can present with limb and cardiac deformity but was ruled out of diagnosis as there was absence of other congenital deformities like vertebral deformity, anorectal malformation, tracheoesophageal fistula, or renal anomalies.[15]

Family screening, which involves X-rays of the hands and electrocardiograms is important, even when there are no apparent clinical deformities. It is essential to offer counseling to parents since this condition is genetically inherited in autosomal dominant manner with a high degree of penetrance. Additionally, early detection of cardiac abnormalities is crucial to correct them at an early stage, thereby extending the lifespan of affected individuals.

CONCLUSIONS

Holt-Oram syndrome is a rarely seen congenital condition characterized by a combination of upper-limb deformities and cardiac abnormalities. This case was reported with the aim to describe the typical features of Holt-Oram syndrome and to emphasize the importance of early detection and intervention for structural cardiac defects. Timely management of both cardiac and orthopedic aspects can significantly enhance the quality of life for affected children, enabling them to lead normal lives. All newborns with upper-limb deformities should be assessed for potential cardiac issues to facilitate early intervention.

Genetic counseling should be done for families affected by Holt-Oram syndrome (HOS) due to its autosomal dominant inheritance pattern. This pattern means that each affected individual has a 50% chance of passing the TBX5 mutation to their children. Genetic

counseling can help families understand the risk of inheritance, the potential variability in disease presentation, and the benefits of genetic testing. They also assist with family planning decisions, prenatal testing options, and the emotional aspects of managing a genetic condition.

CONFLICT OF INTEREST

None

SOURCES OF FUNDING

None

REFRENCES

1. Holt M, Oram S. Familial heart disease with skeletal malformations. British heart journal. 1960 Apr;22(2):236. [DOI]
2. Huang T. Current advances in Holt-Oram syndrome. Current Opinion in Pediatrics. 2002 Dec 1;14(6):691-5.[Full Text]
3. Vanlerberghe C, Jourdain AS, Ghoumid J, Frenois F, Mezel A, Vaksmann G, et al. Holt-Oram syndrome: clinical and molecular description of 78 patients with TBX5 variants. European Journal of Human Genetics. 2019 Mar;27(3):360-8.[DOI]
4. Mori AD, Bruneau BG. TBX5 mutations and congenital heart disease: Holt-Oram syndrome revealed. Current opinion in cardiology. 2004 May 1;19(3):211-5.[Full Text]
5. Sinha R, Nema D. Rare cardiac defect in Holt-Oram syndrome: online article. Cardiovascular journal of Africa. 2012 Mar 1;23(2):3-4.[DOI]
6. McDermott DA, Fong JC, Basson CT. Holt-Oram Syndrome. 2004 Jul 20 [Updated 2019 May 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.[Full Text]
7. Hurst JA, Hall CM, Baraitser M. The Holt-Oram syndrome. Journal of medical genetics. 1991 Jun;28(6):406.[DOI]
8. Basson CT, Huang T, Lin RC, Bachinsky DR, Weremowicz S, Vaglio A, et al. Different TBX5 interactions in heart and limb defined by Holt–Oram syndrome mutations. Proceedings of the National Academy of Sciences. 1999 Mar 16;96(6):2919-24.[DOI]
9. Bruneau BG, Logan M, Davis N, Levi T, Tabin CJ, Seidman JG, et al. Chamber-specific cardiac expression of Tbx5 and heart defects in Holt–Oram syndrome. Developmental biology. 1999 Jul 1;211(1):100-8.[DOI]
10. Basson CT, Cowley GS, Solomon SD, Weissman B, Poznanski AK, Traill TA, et al. The clinical and genetic spectrum of the Holt-Oram syndrome (heart-hand syndrome). New England Journal of Medicine. 1994 Mar 31;330(13):885-91.[Full Text]
11. National Center for Biotechnology Information. TBX5 T-box transcription factor 5 [Gene]. NCBI Gene.[Full Text]
12. Bossert T, Walther T, Gummert J, Hubald R, Kostelka M, Mohr FW. Cardiac malformations associated with the Holt-Oram syndrome-report on a family and review of the literature. The Thoracic and Cardiovascular Surgeon. 2002 Oct;50(05):312-4.[Full Text]
13. Newbury-Ecob RA, Leanage R, Raeburn JA, Young ID. Holt-Oram syndrome: a clinical genetic study. Journal of medical genetics. 1996 Apr 1;33(4):300-7.[DOI]

14. Sharma P, Sharma N, Sharma D. A narrative review on fanconi anemia: genetic and diagnostic considerations. Global Medical Genetics. 2022 Sep;9(03):237-41.[Full Text]
15. Pariza PC, Stavarache I, Dumitru VA, Munteanu O, Georgescu TA, Varlas V, Gheorghe CM, Bohîlțea RE. VACTERL association in a fetus with multiple congenital malformations–Case report. Journal of Medicine and Life. 2021 Nov;14(6):862.[DOI]