ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 12 | December - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A RARE CASE REPORT OF HOLT-ORAM SYNDROME IN A NEWBORN FROM WEST BENGAL, INDIA.

Neonatology

Dr. Deblina Patra Junior Resident, Department of Paediatrics, Burdwan Medical College, West Bengal.

Dr. Ritajyoti Ghosh Junior Resident, Department of Paediatrics, Burdwan Medical College, West Bengal.

Dr. Sarbik Sarkar Junior Resident, Department of Paediatrics, Burdwan Medical College, West Bengal.

Dr. Aizuddin Sk Junior resident, Department of Paediatrics, Burdwan Medical College, West Bengal.

Prof .Tarak Nath Ghosh Professor, Department of Paediatrics, Burdwan Medical College ,West Bengal.

Dr. Sumanta Laha* Associate professor, Department of Paediatrics, Burdwan Medical College, West Bengal. *Corresponding Author

ABSTRACT

Holt–Oram syndrome or heart- hand syndrome is a rare autosomal dominant genetic disorder with skeletal abnormality of upper limbs and congenital heart disorders like Atrial Septal Defect(ASD), Ventricular Septal Defect(VSD) or cardiac conduction defect. Mutations in THX5 gene can disrupt the normal development of these structures, leading to the characteristic features of this syndrome. We present a case of Holt–Oram syndrome in a newborn with absence of thumbs in both hands, bilateral curved radius and congenital heart defect of Ostium Secundum Atrial Septal Defect. This case report emphasizes the importance of evaluation of every newborn for possible congenital heart disease, who presented with thumb or upper limb anomalies.

KEYWORDS

Holt-Oram syndrome, Newborn, Thumb, Ostium Secundum Atrial Septal Defect.

INTRODUCTION

Holt-Oram syndrome is a rare genetic disorder characterized by developmental abnormalities in the upper limbs and the heart. It was first described by Mary Holt and Samuel Oram in 1960 [1] and is estimated to occur in approximately 1 in 100,000 live birth[2-4]. The syndrome is caused by mutations in the TBX5 gene, which is responsible for the development of the heart and upper limb structures. Patients with Holt-Oram syndrome typically exhibit skeletal abnormalities, such as absent or malformed thumb and radial bone, as well as congenital heart defects.[4-7] Recent research has focused on understanding the genetic basis of this syndrome, particularly the role of mutations in the TBX5 gene. TBX5 is a transcription factor that plays a crucial role in the development of the heart and upper limbs. Mutations in this gene can disrupt the normal development of these structures, leading to the characteristic features of Holt-Oram syndrome.[8] Studies have identified a variety of mutations in the TBX5 gene, including missense, frameshift, and nonsense mutations, as well as large-scale deletions and duplications. These mutations typically result in a loss of TBX5 function or a dominant-negative effect, interfering with the regulatory activities of the protein. The precise mechanisms by which TBX5 mutations lead to the phenotypic manifestations of Holt-Oram syndrome are still being elucidated, but research suggests that they may disrupt the expression of genes involved in limb and heart development.[8,9]

In pediatric patients with Holt-Oram syndrome, there are distinct clinical manifestations involving both cardiac and upper limb abnormalities. Atrial septal defects (ASD) and ventricular septal defects (VSD) are the most prevalent cardiac anomaly presenting with respiratory distress, repeated chest infection or heart failure. Few cases may have complex congenital heart defect or cardiac conduction defect presenting with sinus bradycardia or first degree AV block at birth. Furthermore, upper limb abnormalities such as absence or underdevelopment of the thumb, or hypothenar muscles, restricts the grasp and pinch functions of the hand. Additionally, malformations of the radius bone like aplasia or hypoplasia can result in unequal arm length , reduced strength and stability in the upper limb, further impairing the child's motor functions.[10-12] Here, we present one of the rarely reported cases of pediatric Holt-Oram syndrome in India.

Case Report

A full term female newborn was born to a 24 years old primigravida by vaginal delivery with birth weight of 2.4 kg and uneventful postnatal period. There was no history of consanguinity in parents. On general examination, the newborn had upper limb deformity with absence of thumbs in both hands [Figure 1].Both lower limbs were normal. No other deformity was noted in head to toe examination . During the hospital course, the newborn developed respiratory distress with tachypnea and subcostal and intercostal retraction. Examination revealed bilateral crepitations, hepatomegaly and ejection systolic murmurs on auscultation. Chest radiographs showed signs of pneumonia with cardiomegaly and X-ray of upper limb showed the bilateral curved radius[Figure 2].The echocardiography showed Ostium Secundum Atrial Septal Defect (OSASD). The diagnosis of Holt Oram syndrome was made based on the clinical criteria. The genetic testing could not be done because of the lack of suitable infrastructure. The baby was managed with moist oxygen, intravenous antibiotics and frusemide. An orthopedic opinion was sought, and conservative management was advised. The patient was reviewed after 30 days, and was found to be doing well. For OSASD, cardiac surgery was planned, and the patient was put on prophylaxis for infective endocarditis.

Figure 1: Absence of Thumbs in Both Hands.

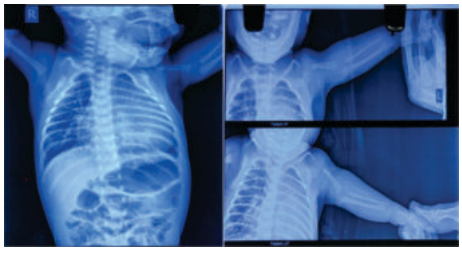

Figure 2: Radiographic Evidence of Pneumonia With Cardiomegaly and Bilateral Curved Radius.

DISCUSSION

The diagnosis of Holt-Oram syndrome in pediatric patients poses several challenges and requires careful consideration due to its overlapping clinical features with other syndromes and diseases. Firstly, the presence of cardiac abnormalities including congenital heart defects is a hallmark of Holt-Oram syndrome, but these cardiac abnormalities can also be seen in various other genetic syndromes. Therefore, it is essential for clinicians to conduct a thorough evaluation of the cardiac manifestations in order to differentiate Holt-Oram syndrome from other similar conditions. Secondly, the skeletal abnormalities, particularly upper limb abnormalities such as absent or hypoplastic thumbs, are characteristic findings in Holt-Oram syndrome.[13-16] However, these skeletal anomalies can also be seen in isolated upper limb defects or other genetic disorders, further complicating the differential diagnosis. Additionally, the variability in the phenotypic expression of Holt-Oram syndrome makes the diagnosis even more challenging, as some patients may present with subtle or atypical features that overlap with other syndromes. Therefore, genetic testing including sequencing of the TBX5 gene, which is known to be associated with Holt-Oram syndrome, is crucial in confirming the diagnosis and ruling out other genetic conditions. Overall, the diagnosis and differential diagnosis of Holt- Oram syndrome in pediatric patients require a comprehensive assessment of cardiac and skeletal abnormalities, as well as consideration of the phenotypic variability and genetic testing to arrive at an accurate diagnosis.[17,18]

Surgical interventions have proven to be efficacious in the management of Holt-Oram syndrome in pediatric patients. Various surgical strategies, including corrective and palliative procedures, have been employed to address the cardiac anomalies associated with this syndrome. These interventions aim to improve heart function, relieve symptoms, and enhance the quality of life for affected individuals. The outcomes of these surgeries have generally been positive, with significant improvements in cardiac function and symptom relief observed in most cases. However, the success of these interventions is heavily dependent on several factors, including the severity of the cardiac defects, the age of the patient, and the presence of other associated abnormalities.[19,20] Family screening with hand X-ray and ECG should be done as it is a autosomal dominant disorder. Goal of management should include to provide some function to defective upper limb by surgery or physiotherapy and to detect cardiac defect early and manage accordingly.

CONCLUSION

Advancements in genetic research have shed light on the underlying molecular mechanisms of the syndrome and have identified specific genetic variations that contribute to its development. These findings offer opportunities for targeted therapies and personalized medicine approaches tailored to the unique genetic profiles of patients with Holt-Oram syndrome. Additionally, preventive measures such as genetic counseling and prenatal screening have the potential to identify individuals at risk and empower them with the knowledge to make informed decision regarding family planning. Further research in understanding the complex interplay between genetic and environmental factors will contribute to the development of effective prevention strategies and improved management of Holt-Oram syndrome in pediatric patients. Thus all newborns with upper limb anomaly should be screened for any cardiac defect as its early detection can reduce the morbidity and mortality of this rare genetic disease.

REFERENCES

1. Holt M, Oram S. Familial heart disease with skeletal malformations. Br Heart J 1960; 22(2): 236-42.
2. Bohm J, Heinritz W, Craig A, Vujic M, Ekman-Joelsson BM, Kohlhase J, et al. Functional analysis of the novel TBX5 c.1333delC mutation resulting in an extended TBX5 protein. BMC Med Genet 2008; 9: 88.
3. Garne E. Evaluation of prenatal diagnosis of congenital anomalies by fetal ultrasonographic examination. Ultrasound Obst Gyn 2001; 17: 386-91.
4. Forster UG, Kujat MA. Genotype-Phenotype correlation in Holt-Oram Syndrome. Leipzig: Institut fuer Humangenetik-Leipzig; 2001.
5. 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. Proc Natl Acad Sci U S A 1999;96(6): 2919-24.
6. 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). N Engl J Med 1994; 330(13): 885-91.
7. Bonnet D, Pelet A, Legeai-Mallet L, Sidi D, Mathieu M, Parent P, et al. A gene for Holt-Oram syndrome maps to the distal long arm of chromosome 12. Nat Genet 1994; 6(4): 405-8.
8. Brown DD, Martz SN, Binder O, Goetz SC, Price BM, Smith JC, et al. Tbx5 and Tbx20 act synergistically to control vertebrate heart morphogenesis. Development 2005; 132(3): 553-63.
9. Stoll C, Alembik Y, Dott B, Roth MP. Associated malformations in patients with limb reduction deficiencies. Eur J Med Genet 2010; 53(5): 286-90
10. Stoll C, Garne E, Clementi M. Evaluation of prenatal diagnosis of associated congenital heart diseases by fetal ultrasonographic examination in Europe. Prenat Diagn 2001; 21(4): 243- 52.
11. 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; 211: 100-108.
12. Webb G, Gatzoulis MA; Congenital Heart Disease for the Adult Cardiologist. Atrial Septal Defects in the Adult: Recent Progress and Overview. Circulation. 2006; 114: 1645-1653.
13. Wall LB, Piper SL, Habenicht R, Oishi SN, Ezaki M, Goldfarb CA. Defining features of the upper extremity in Holt-Oram syndrome. J Hand Surg Am 2015;40:1764-8.
14. Garg V, Bajaj M, Sharma A. A rare case report of newborn with Holt-Oram syndrome. International Journal of Science & Healthcare Research. 2020; 5(2): 77-80.
15. Najjar H, Mardini M, Tabbaa R, Nyhan WL. Variability of the Holt-Oram syndrome in Saudi individuals. Am J Med Genet 1988; 29(4): 851-5.
16. Kohlhase J, Heinrich M, Schubert L, Liebers M, Kispert A, Laccone F, et al. Okihiro syndrome is caused by SALL4 mutations. Hum Mol Genet 2002; 11(23): 2979-87.
17. Saura D, Campos JV, Villegas M, Pico F, de la MG, Valdes-Chavarri M. Heart-hand syndrome. Int J Cardiol 2008 16; 129(1): e7-e9.
18. Clementi M, Tenconi R, Bianchi F, Stoll C. Evaluation of prenatal diagnosis of cleft lip with or without cleft palate and cleft palate by ultrasound: experience from 20 European registries. EUROSCAN study group. Prenat Diagn 2000; 20(11): 870-5.
19. Spiridon MR, Petris AO, Gorduza EV, Petras AS, Popescu R, Caba L: Holt-Oram syndrome with multiplecardiac abnormalities. Cardiol Res. 2018;9:324-9.
20. McDermott DA, Bressan MC, He J, Lee JS, Aftimos S, Brueckner M, et al. TBX5 genetic testing validates strict clinical criteria for Holt-Oram syndrome. Pediatr Res 2005;58:981-6.