Research Paper Medical Science

# Holt Oram Syndrome - Case Report


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| **Dr.Santosh kumar swami** | PG Resident, Dept. Of Pediatrics, Govt. Medical college KOTA |
| **Dr.Suraj Singh** | PG Resident, Dept. Of Pediatrics, Govt. Medical college KOTA |
| **Dr. A. L. Bairwa** | Professor, Dept. Of Pediatrics, Govt. Medical college KOTA |


**ABSTRACT**

The Holt–Oram syndrome or atriodigital dysplasia is an autosomal dominant disorder with near complete penetrance and variable expression, caused by mutations of the TBX5 gene (12q24.1), affecting one in 100 000 live births. 60% of cases are familial and 40% sporadic. We present the case of a 8 months old male patient presented with respiratory problem .Patient had characteristic right sided hand deformity . Further evaluation confirmed it Holt oram syndrome.

**KEYWORDS**: Holt-Oram syndrome [HOS]. Disease name and synonyms --Holt-Oram syndrome (HOS) Atriodigital dysplasia ,Heart-hand syndrome (1)

**Introduction:-**

The Holt–Oram syndrome (HOS) is a developmental disorder of the heart and upper limbs, first described by Holt and Oram in 1960 affecting one in 100 000 live births; 40% of cases are sporadic [2].

Phenotypic features are represented by upper limb defects ranging from phocomelia to minor thumb anomalies and cardiac defects in 50–95% of cases, most often an ostium secundum type atrial septal defect and conduction anomalies; some patients have ocular defects and absence of the pectoralis major [3].

The responsible gene – TBX5 is located on12q24.1 [ 4,5] and belongs to the T-box gene family, which encodes a large family of transcription factors (more than 20 members identified in humans), with key role in embryonic development (differentiation of posterior mesoderm and axial development, control of the proper migration and modulation of adhesive properties of early embryonic cells). TBX5acts synergistically with NKX2-5 and promotes cardiomyocytes differentiation by binding to the promoter of the gene encoding cardiac-specific natriuretic peptide precursor type A (NPPA) [6]. TBX5 also interact with GATA4[7] and TAZ [8]. Another target of TBX5 is connexin 40, expression of which is important for the conduction of electrical impulses throughout the heart [9]. Target genes are also several cardiac-expressed genes including cardiac alpha-actin, atrial natriuretic factor, cardiac myosin chains and SALL4. TBX5 and SALL4 interact both positively and negatively to regulate the patterning and morphogenesis of the forelimb and heart [10] SALL4mutations are responsible for the Duane radial ray syndrome [11].

More than 34 different mutations have been described, some of them reducing the DNA-binding activity of TBX5and others generating loss of synergy in transcriptional activation between TBX5and NKX2.5[12]. The null mutations cause severe cardiac and skeletal phenotypes and missense mutations affect differently the heart and the limbs [13]. Patients with limb or heart defects alone may bear offspring with the complete syndrome [14].

**CASE REPORT:-**

We present a case of a 8 months old male child admitted in our hospital for respiratory problem. He was second child of nonconsangualy married couple. His parents and elder female sibling was normal. No history of any drug exposure during pregnancy was obtained .He was hospitalised 1st time ever l

Life for respiratory problem.Physical examination revealed characteristic [Absent thumb and radial deviation of hand] right hand deformity [fig:1] i.e. Radial club hand, which was present since birth. X-ray of affected hand [fig:2] showed absence of radius , and thumb agenesis. No any other external congenital abnormality was detected.

On cardiac auscultation a murmur was appreciated in left side of sternum. Chest x-ray showed cardiomegaly . ECG showed right ventricular hypertrophy but no conduction defect was noted. Echocardiography identified an ostium secundum type atrial septal defect with significant left to right shunt. Hemogram was within normal limits [ Hemoglobin-10.6,Platelet count- 4.91 lace] & USG Abdomen did not revealed any abnormality .Renal and liver function tests also were normal.

Thumb deformity was corrected surgically and Patient was advised to consult pediatric cardiologist for ASD correction. Karyotype and genotype study was not available.



**Fig:1 , Characteristic Right limb**



**Fig:2, X-ray of affected limb**

**Disscussion:-**

The association of upper limb anomalies with atrial septal defect was suggestive for the diagnosis of Holt–Oram syndrome. Strict diagnostic criteria for HOS comprise the presence of preaxial radial ray malformation of at least one upper limb along with a personal or a family history of septation defects and/or atrioventricular conduction disease [15]. If this criterion is meet TBX5 mutations are found in 74% of cases.

The case we presented seems to be sporadic because his parents and sister were apparently healthy but minor heart or limb defects could be revealed only by echocardiography and radiological examination, which were not performed in his first-degree relatives.

In HOS, radial ray development is abnormal and, although bilateral, the left side is more significantly affected [14]. But in contrast to this in our patient right side was affected.

The thumb is the most commonly affected structure (it can be absent, hypoplastic or triphalanged) and is usually associated with hypoplastic thenar or limited supination of the forearm. Severity ranges from phocomelia to clinodactily, limited supination and sloping shoulders. Radial hypoplasia ranges from complete absence (in this case ulnar ray development may be affected too) to mild hypoplasia that can be detected only by radiograph. Hypoplasia of the shoulders, clavicles and humerus had also been reported. Associated muscular hypoplasia of the forelimb correlates with the severity of skeletal involvement. There is also a positive correlation between the severity of the limb and cardiac defects and both cardiac and limb defects are more severe in sporadic cases [2]. Skeletal features in the presented case were radial and thumb agenesis of right upper limb.Cardiac involvement was typical for HOS. Analysis of the literature showed that single cardiovascular malformations such as atrial septal defect, ventricular septal defect, patent ductus arteriosuswere reported in 66% of cases while 17.5% of patients had more complex cardiac defects (hypoplastic left heart, total anomalous pulmonary venous return, endocardial cushion defects, truncus arteriosus) [16].

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