Case Report

Heart–Hand Syndrome Type 1: A Case Report with Literature Review

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ABSTRACT

Holt-Oram syndrome (HOS) is the most common form of heart–hand syndromes and is inherited in an autosomal dominant fashion. It is characterized by the presence of upper limb and cardiac anomalies. A little more than 300 case reports have been published with various clinical features of HOS, even though the prevalence is as rare as 1 in 100,000 live births. We present here a young infant with not only upper limb and cardiac abnormalities, clinically diagnosed as HOS, but also with a minor lower limb anomaly. The related literature of clinical importance is also discussed.

Keywords: Congenital heart disease, Heart–hand syndrome, Holt-Oram syndrome

Heart–hand syndromes are a set of rare diseases which present clinically with heart and limb abnormalities and have an approximate prevalence of 1 in 100,000 live births [1-3]. They are of six types as of July 2013, namely: Holt-Oram syndrome (HOS), Berk–Tabatznik syndrome, heart–hand syndrome type 3, brachydactyly-long thumb syndrome, patent ductus arteriosus-bicuspid aortic valve syndrome, and heart–hand syndrome, Slovenian type [4]. Heart–hand syndrome type 1, commonly known as Holt-Oram syndrome (OMIM 142900) and also the most common type, is an autosomal dominant disorder with almost complete penetrance but variability in expression. It was first described by Mary Holt and Samuel Oram in 1960 when they identified thumb anomalies and atrial septal defect in family members across four generations [5, 6]. It is caused by a mutation in the TBX5 gene located on chromosome 12q24.1 and is associated with variable phenotypes with a wide clinical spectrum, ranging from subclinical radiologic findings to life-threatening disease due to cardiac anomalies including atrial and ventricular septal defects and conduction disorders [7].

CASE REPORT

A 6-month-old male baby born to a non-consanguineously married couple was admitted to our pediatric ward with a diagnosis of bronchopneumonia and culture-proven urinary tract infection. He was born to a 27-year-old primigravida mother, with an uneventful antenatal history, by full-term normal delivery, with a birth weight of 3.5 kg and uneventful postnatal history. His growth and milestones of development were normal. He was immunized to date according to the National Immunization Program.

Clinical examination revealed a normal sized head with wide anterior fontanel (3 × 3 cm^2) and no facial dysmorphism except for long philtrum and low set ears. There was hypoplasia of the left thenar eminence, absence of the first metacarpal, and triphalangeal thumb on the left side (Fig. 1). The right upper limb was normal. However, unlike described in the literature, the baby also had an additional lower limb anomaly, as evidenced by the overlapping of the second and fourth toes over adjacent toes. The trunk, abdomen, and spine were normal. Systemic examination revealed a short systolic murmur of Grade 2/6, heard best at the left lower sternal border.

2D Echocardiogram (ECHO) done at birth had shown moderate ventricular septal defect (VSD) and restrictive ostium secundum atrial septal defect (ASD) with moderate pulmonary artery hypertension. Repeat 2D ECHO done during this admission was normal with natural closure of both ASD and VSD, and normal pulmonary artery pressure. X-ray of upper limbs confirmed the clinical findings (Fig. 2). Electrocardiogram was normal. In view of limb and heart involvement, a clinical diagnosis of HOS was made, on the basis of the clinical criteria for diagnosis. Karyotyping of the child revealed an unconfirmatory clumping of chromosomes. Further, genetic tests could not be done due to

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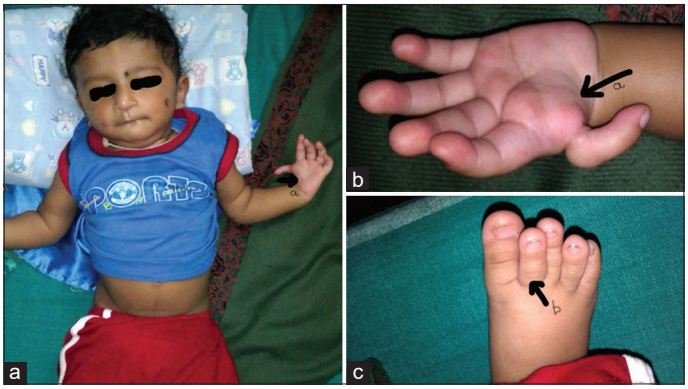

Figure 1: Facial features of the baby showing (a) hypoplasia of the left thenar eminence and (b) overlapping of the second and fourth toes over adjacent toes.

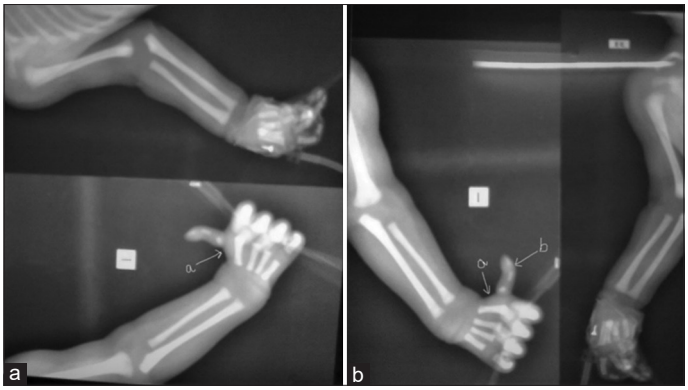

Figure 2: X-ray of the left upper limb showing (a) absent left first metacarpal and (b) triphalangeal thumb

the financial constraints of parents. Parents and other members of the family including two generations were normal, except the maternal uncle who had right upper limb pre-axial polydactyly.

We referred the child to an orthopedician for further management and also for occupational therapy. Orthopedician advised reconstructive surgery for the left wrist and thumb. However, the parents were not willing for the same. The child was on irregular occupational therapy for some time but was lost for follow-up after 6 months. Still, the prognosis in this child would be good except for the discomfort using the left upper limb, as he was developmentally normal and his cardiac septal defects had closed naturally.

DISCUSSION

All patients with HOS have upper limb anomaly and about 85%–95% have cardiac malformation [8, 9]. Skeletal abnormalities affect the upper limbs exclusively and lower limb abnormalities have not been reported [8]. However, our child presented here had a lower limb anomaly also, as shown by the overlapping of toes.

Hence, this case is being presented here not only because of its rarity which prompts meticulous clinical examination but also the presence of a lower limb anomaly, even though a minor one.

The upper limb anomalies usually present as a spectrum and from minor abnormalities such as clinodactyly of the fingers, limited supination of the forearms, and sloping shoulders to severe ones being reduction deformities, including phocomelia and ectromelia [8]. Poznanski *et al*. demonstrated that carpal abnormalities are more specific for HOS than those of the thumb [10]. Ostium secundum type ASD and VSD are the most common heart defects. Other cardiac defects range from asymptomatic conduction disturbances (first-degree heart block) to multiple structural defects. Almost every type of cardiac anomaly has been reported, either singly or as part of a group of multiple defects. Sudden death from heart block has also been reported [11-13].

Thus, the criteria for clinical diagnosis include either the presence of cardiac malformations, conduction defects, and radial ray abnormalities (or both) in an individual or the presence of radial ray abnormalities with or without cardiac malformations or conduction defects in individuals with a family history of HOS [14]. The family history should be consistent with autosomal dominant inheritance. Moreover, this must be differentiated from other similar autosomal dominant conditions such as [8] Fanconi anemia syndrome, thrombocytopenia-absent radius (TAR syndrome), heart–hand syndrome II, heart–hand syndrome III, Okihiro syndrome, long thumb brachydactyly syndrome, and VACTERL association.

Treatment of upper limb skeletal problems may include corrective or reconstructive surgery, the use of limb prosthetics, and physical or occupational therapies. The goal of treatment is to help people with HOS have as much use of the upper limbs as possible.

TBX5 mutations manifest as cardiac defects and radial ray upper limb abnormalities ranging from pre-axial (thumb) polydactyly, triphalangeal, or absent thumb to phocomelia. However, ulnar ray defects (postaxial) are less common manifestations of the syndrome [8]. A wide variety of mutations can cause HOS, resulting in multitudinous phenotypes. Null allele mutations apparently cause significant limb and cardiac malformations, while some missense mutations might cause more severe cardiac defects [9]. It is known that the upper extremity malformations are fully penetrant, but congenital heart defects occur in approximately 75% of affected individuals [9]. Hence, it would be essential to look for cardiac defects in any child with limb anomalies.

CONCLUSION

It is reemphasized that early identification of cardiac problems in a child with upper limb defects and appropriate management would decrease morbidity and mortality. Management of these children requires a multidisciplinary team approach including pediatrician, cardiologist, cardiothoracic surgeon, orthopedician, and occupational therapist so that early rehabilitation would improve the quality of life in them. It would with worthwhile to look for a lower limb anomaly also as was present in our child, even though it is not mentioned in literature till date."

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