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Unusual Hand Malformation with Cardiac Defect: A Rare Presentation

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ABSTRACT Congenital heart defects occurring together with upper limb malformations as a group of dominantly inherited disorders constitute the Heart-Hand syndrome (HHS) with varied phenotypic manifestations. The researchers report herein a case of HHS Type IV presented with large PDA and cutaneous syndactyly from India. Echocardiography showed large PDA with left to right shunt. Radiograph of the right hands showed features of complete simple cutaneous syndactyly (middle and ring finger) and central type of polydactyly with probable syndactyly (index finger). Karyotype and FISH showed a normal 46,XX. The management of individuals with HHS optimally involves a multidisciplinary team approach, with specialists in genetics, cardiology and orthopaedics including a specialist in hand surgery.

INTRODUCTION

Congenital cardiac defects occurring together with upper limb malformations as a group of dominantly inherited disorders constitute the Heart-Hand syndrome (HHS) with varied phenotypic manifestations. The spectrum of involvement varies from individuals and they are broadly classified as HHS types I-IV. Type I is the most common HHS, which is known as Holt-Oram syndrome (HOS; OMIM 142900). Its incidence is one in 1,00,000 live births, and affects both males and females equally (Barisic et al. 2014). Congenital cardiac defects are seen in about 75 percent of cases of patients with type I HHS; most common defects are atrial and/or ventricular septal defects (ASD/VSD) and atrio ventricular nodal diseases (Postma et al. 2008). Common limb defects in type I HHS is skeletal preaxial radial ray abnormalities that may be unilateral and asymmetrical and can vary from subtle, subclinical findings to frank phocomelia (Garavelli et al. 2008). Type II HHS syndrome is also called as Tabatznik's syndrome which is characterized by upper limb abnormalities like hypoplastic deltoids, skeletal anomalies in the humeri, radii, ulnae, and thenar bones, brachydactyly type D, abnormal number of carpal bones, polydactyly, bifid thumps, bowing of the radius, sloping shoulders, scoliosis, pectus excavatum and congenital manifestations like cardiac arrhythmias, sino atrial tachycardia, right displacement of the heart, cardiomegaly, coarctation, VSD and patent ductus arteriosus (PDA) (Silengo et al. 1990). Type III HHS (OMIM: 140450) (Spanish type) is characterized by cardiac conduction diseases like intraventricular delays, sick sinus syndrome and incomplete bundle-branch block. The skeletal defects in type III are brachydactyly of digit 2-5 which mainly involves hands and feet (Basson et al. 1995). Type IV is variants of HHS. The major cardiac anomalies with HHS IV are pulmonary stenosis, PDA, single atrium and VSD. The skeletal defects in type IV are upper limb polydactyly, natal teeth and cutaneous syndactyly (Muranjan and Bharucha 2000). Herein, the researchers report a rare sporadic case of HHS type IV, with large PDA left to right shunt and upper limb complete simple syndactyly; central type of polydactyly with probable syndactyly as part of the spectrum. To the best of the researchers' knowledge, this is the first case report of HHS type IV from India.

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Case Report

The child was a 1-month-old female, the only offspring born to unaffected non- consanguineous parents. Child was referred to the researchers' hospital for large PDA with left to right shunt, with complaints of interrupted feeding and forehead sweating during feeds. She had been delivered at emergency LSCS surgery for intrauterine growth restriction (IUGR), gestational diabetes mellitus and oligohydraminos. There was no history of teratogen exposure during pregnancy. The child birth weight was 1.8 kg, birth length was 45 cm, and head circumference was 45 cm. She has a pulse rate of 118/min, the blood pressure was 78/59 mmHg and systemic oxygen saturation was 98 percent ambient room air. There was no history of cyanosis and upper respiratory infections. Routine haematological and biochemical investigations were normal. Cardiovascular examination revealed cardiomegaly, S1 normal, S2 split, grade 2 ejection systolic murmur, left 2nd intercoastal space. Electrocardiogram (ECG) showed normal sinus rhythm with ventricular rate 123 bpm, PR interval was 120 msec, QRS axis was +60º, BVH, LAE. Chest X-ray poster anterior view showed levocardia, situssolitus, 60 percent cardiothoracic ratio (mild cardiomegaly), pulmonary plethora. Two dimensional echocardiography (Echo) showed large 6mm PDA shunting left to right, left atrial/left ventricular (LA/LV) volume over load, mild arch gradient of 34/11 mmHg and good biventricular systolic function. Radiography of the right hand showed there is fusion of the skin in between the 3rd and 4th phalanges from the base till the tip of the finger tips (Fig. 1a). No fusion of the bones of 3rd and 4th phalanges, that is, features of complete simple cutaneous syndactyly. In addition, there is a supernumerary digit at the level of the 2nd proximal inter phalangeal joint space. There is fusion of the skin in between the supernumerary digit and the 2nd phalanx which is a feature of central type of polydactyly with probable syndactyly (Fig. 1b). No obvious deformities were observed in lower limbs or elsewhere. Dysmorphic features like low sets ears, flat nasal bridge, protruding tongue and simian crease in left hand were noted and the patient was clinically suspected for Down syndrome (DS). The patient was advised for thyroid function test and karyotyping. Thyroid function tests revealed elevated TSH levels. Karyotyping was conducted by analysis of G-banded chromosomes using 5 mL heparinized peripheral blood sample. Metaphase spreads were made from phytohemagglutinin stimulated peripheral lymphocytes using standard cytogenetic techniques. Cultures were harvested and karyotyping was performed by G-banding using trypsin and Giemsa stain (GTG).

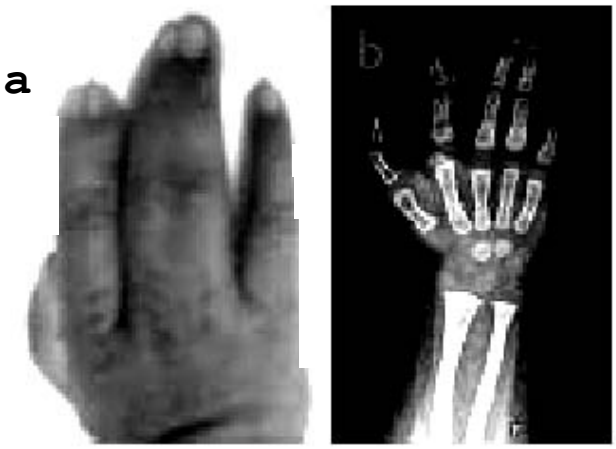

Fig. 1. Figure a is a photograph of patient's right hand and Figure b is radiograph of patient's right hand

The chromosomal status was analysed using CytoVision from Leica Biosystems. 25 metaphases were analysed and the chromosomal analysis revealed apparently normal female karyotype 46,XX. Fluorescent in situ hybridization (FISH) was performed to rule out mosaicism if any. FISH was performed on 20 metaphases and 180 interphase nuclei using LSI 21 probe from Vysis Inc., USA localized to 21q22. The probe hybridization showed the presence of 2 signals for chromosome 21 (red) in all the cells analysed. The patient underwent successful repair or PDA device closure using 6/8 mm PDA device. Post procedure investigation of Echo revealed stable device position, small residual flow from the outer edge of the device with systolic gradient of 34 mmHg and mean gradient of 9 mmHg, good aortic and branch pulmonary artery (PA) flow seen, good biventricular systolic function. The orthopaedic surgery was planned.

DISCUSSION

The cardiac and limb malformations that characterize the relatively rare HHS frequently occur in isolation or in the setting of other multi-organ system congenital disorders that are likely to be genetically heterogeneous and differ in their clinical phenotype and inheritance pattern. HHS I (HOS) and HHS III are autosomal dominant; HHS II (Tabatznik syndrome) is probably X-linked dominant and HHS IV is probably autosomal recessive (Muranjan and Bharucha 2000). The limb defects seen in this patient do not confirm to the patterns described with previously reported syndrome. Muranjan and Bharucha (2000) have reported a variant of heart hand syndrome IV. A 10-year-old child having mesoaxial hexadactyly and syndactyly of the one hand and postaxial polydactyly of the other. The researchers' patient had complete simple syndactyly and central type of polydactyly with probable syndactyly in one hand. The presence of syndactyly and polydactyly confirms to the original descriptions of the hand malformation in HHS IV. Skeletal abnormalities rarely involve the lower limbs. In this case also no obvious deformities were observed in lower limbs or elsewhere. This is because the mutant gene interferes with the embryonic differentiation during the 4th and 5th weeks of pregnancy, when the lower limbs are not differentiated (Kumar et al. 2014). A group of transcription factors, including the homeodomain protein Nkx2-5, GATA family zinc finger proteins GATA4, 5, and 6, MEF2 factors and SRF (MADS box proteins), T-box factors, including Tbx1, Tbx2, Tbx3, Tbx5, Tbx18, and Tbx20, and the Lim-homeodomain protein Isl1, are critical for heart development. The core cardiac transcription factors function in a mutually reinforcing transcriptional network in which each of the factors regulate the expression of the others (He et al. 2011). Several of the core factors involved in heart development also function as biochemical partners for each other, reflecting a complex molecular and genetic interplay controlling multiple stages of heart and conduction system development. Several gene families are involved in the spatially and temporally co-ordinated growth and differentiation of the developing limb. HOX genes are evolutionarily highly conserved and encode transcription factors of fundamental importance for body patterning. This gives a high degree of specificity to the promoter region and is fundamental to the control of the patterning process in the developing limb (Barham and Clarke 2008). Tbx5 and Tbx4 are T-box family transcription factors expressed in the forelimb and hind limb, respectively. The majority of cases of HOS result from new mutations in the Tbx5 gene (Nourzad and Baghershiroodi 2011). The major cardiac anomalies with HHS IV are pulmonary stenosis, PDA, single atrium and VSD (Muranjan and Bharucha 2000). The researchers' patient had only large PDA with left to right shunt. Apart from facial dysmorphism none of the other features were noted in the researchers' patient. Whole-exome sequencing (WES) studies are now underway to identify the definitive cause of this rare genetic disease.

CONCLUSION

HHS is a rare disorder and little is known about its prognosis. Current study shows that prognosis depends on the severity of the cardiac and skeletal manifestations; patient with severe morphological manifestations may need surgery, device implantation or specific therapy. The management of individuals with HHS optimally involves a multidisciplinary team approach, with specialists in genetics, paediatric cardiology and orthopaedic, including a specialist in hand surgery. A further genetic analysis with special reference to exome sequencing is underway on HHS which will elucidate basic

mechanisms underlying cardiac morphogenesis, and clarify diagnostic and potentially therapeutic approaches.

CONSENT

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

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