

Holt-Oram Syndrome: A Variety of Heart-Hand Syndrome

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Abstract:

Holt-Oram syndrome (HOS) is a heart-upper limb malformation complex, is a rare autosomal dominant disorder, caused by a mutation in the TBX5 gene located on chromosome 12 and near complete penetrance but variable expression. Holt and Oram first described this syndrome in 1960. Approximately 40% of cases represent new mutations. The syndrome is associated with defective development of cardiac structures that results in atrial septal defect (ASD), most commonly the secundum type; heart block of varying degree or both. The syndrome is characterized by cardiac malformations and aplasia or hypoplasia of the thumb. The incidence of HOS is estimated at 1:100,000 live births. In the literature, it is also known as atriodigital syndrome, heart-hand syndrome, upper limb-cardiovascular syndrome, cardiac-limb syndrome, or cardiomeelic syndrome. Herein, we report a 45-year-old female case of HOS presenting a large ostium secundum type ASD along with congenitally fusion of carpal bones in both hands and absence of right first metacarpal bone with triphalagial thumb where as hypoplastic proximal phalange. In left hand, hypoplastic first metacarpal bone and hypoplastic thumb with syndactyly of both thumb with index finger.

Keywords: Holt- Oram syndrome, Atrial Septal Defect.

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Introduction

Holt-Oram syndrome (HOS) is a heart-upper limb malformation complex, is a rare autosomal dominant disorder, caused by a mutation in the *TBX5* gene located on chromosome 12 and near complete penetrance but variable expression. Holt and Oram first described this syndrome in 1960. In the literature, it is also known as atriodigital syndrome, heart-hand syndrome, upper limb-cardiovascular syndrome, cardiac-limb syndrome, or cardiomeelic syndrome. Approximately 40% of cases represent new mutations. The syndrome is associated with defective development of cardiac structures that results in atrial septal defect (ASD), most commonly the secundum type; heart block of varying degree or both. The syndrome is characterized by cardiac malformations and aplasia or hypoplasia of the thumb. Since clinical manifestations may be subtle, the diagnosis may only be made later in life or even missed.

Case Report

We present a case of 45-year-old female patient was admitted to our University Cardiac Center inpatient department with a complaint of palpitation for a year. The patient who was diagnosed with ASD with upper limb deformity was hospitalized for further evaluation and plan of management. Her medical history was non-specific, except palpitation. Her family history was also

non-remarkable. She was delivered by normal vaginal delivery with no history of intrauterine infection. Her vital signs were normal. Pulmonary component of second heart sound palpable, left parasternal lift, epigastric pulsation, loud P₂, splitting of the second heart sound present and a grade 3/6 ejection murmur present, loudest at the anterior sternal border. The other findings were normal. Musculoskeletal findings indicated hypoplasia of the thenar muscles of both hand, both wrist joints were hypoplastic, hypoplastic thumb with syndactyly of thumb and index finger of both hand with functionally hypoactive hand (Fig:1).

Electrocardiography demonstrated a normal sinus rhythm (72 bpm) with features of right ventricular hypertrophy with first degree AV block (Fig: 2).



Fig.-1



Fig.-2

Chest X-ray showed levocardia, a significantly increased cardiothoracic ratio due to the right ventricular hypertrophy, and pulmonary parenchymal changes secondary to moderate pulmonary hypertension. In addition, thoracic X-ray images showed mild kyphoscoliosis(Fig:3). Plain radiographs of both upper limbs showed fusion of carpal bones in both hands and absence of right first metacarpal bone with triphalangeal right thumb where as proximal phalange is hypoplastic and the right thumb morphologically fused with right index finger. In left hand, hypoplastic first metacarpal bone and hypoplastic thumb fused wth left index finger.(Fig: 4,5). Laboratory test results were within reference ranges.



Fig.-4



Fig.-3



Fig.-5

Two-dimensional transthoracic echocardiography revealed an ejection fraction of 58% with a large secundum type ASD (34 mm) in the interatrial septum (Arrow mark), severe tricuspid regurgitation, severe right atrial and ventricular dilation, a pulmonary artery pressure of 56 mmHg. (Fig: 6,7,8)

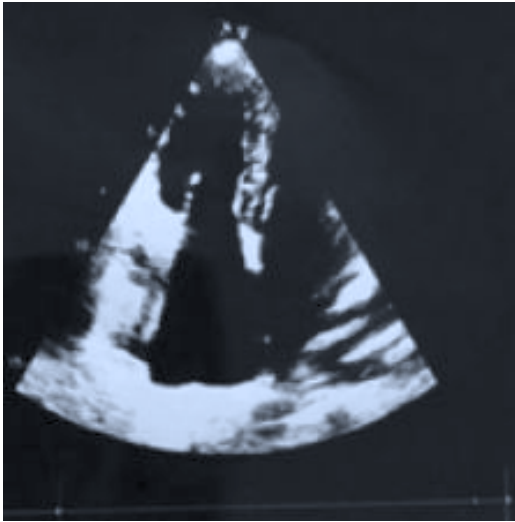


Fig.-6

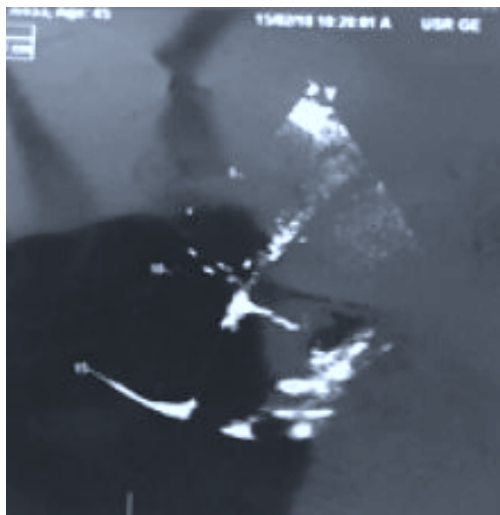


Fig.-7

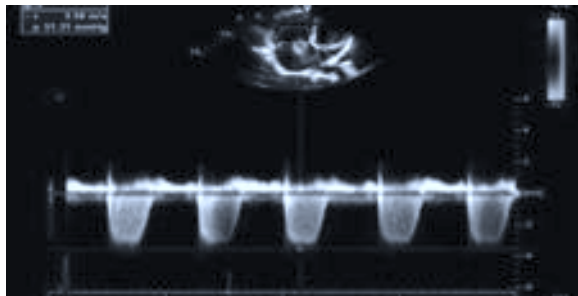


Fig.-8

Based on these findings, cardiovascular surgeons and cardiologists decided that the patient was ineligible for percutaneous intervention and was scheduled for a complete correction surgery.

Discussion:

HOS was first described in 1960 by Mary Holt and Samuel Oram.^{1,2} In a four-generation family with atrial septal defects and thumb abnormalities.¹⁻³ It is a rare disorder with a prevalence of one case per 1,00 000 births in the USA.⁴⁻⁶ It is an autosomal dominant condition⁴⁻⁸ with genetic heterogeneity, but the most common mutations,⁷ present in 70% of patients with clinical diagnosis,⁹ are in the *TBX5* gene of the T-box complex, located on chromosome 12 (12q 24.1), which encodes a transcription factor⁷ that is important in the development of both the heart and upper limbs.⁴ Although most cases are of familial transmission, the literature describes cases due to new mutations^{6,8} in 40—85% of cases. Clinical manifestations are variable, but upper limb abnormalities are always present. Defective development of the embryonic radial axis (e.g. aplasia, hypoplasia, fusion, or other anomalous development) results in a wide spectrum

of phenotypes, including triphalangeal or absent thumbs, foreshortened arms and phocomelia (a malformation in which the hands are attached close to the body; also termed pseudothalidomide syndrome).^{5,8} Abnormalities may be unilateral or bilateral and asymmetric, and may involve the radial, carpal, and thenar bones. Left-sided hand and arm abnormalities are often more severe than right-sided ones.⁵

The most prevalent findings in patients with HOS are malformations or fusions of the carpal bones. Carpal bone abnormalities are the only findings present in every affected individual, although these anomalies may be evident only radiographically in some patients.⁵ Other radiographic abnormalities include posteriorly and laterally protuberant medial epicondyles of the humerus, hypoplastic clavicles, shortened radius and ulnar hypoplasia (occurring only in patients with radial defects).⁵ Clinical recognition of subtle limb anomalies in patients with HOS may require both physical examination and radiographs of the upper extremities,⁵ and assessment of these patients should include lower limb X-ray, since lower limb abnormalities exclude the diagnosis. The most common alterations have been described earlier. Individuals without carpal bone abnormalities in the preaxial radial bones do not have HOS.

In the present case the patient had evident abnormalities of both upper limbs since birth that was subsequently confirmed by typical radiographic findings, with morphological changes to the proximal carpal row of the right hand, right first metacarpal bone is absent where as left one is hypoplastic. Right thumb is triphalangeal and syndactyly between the 1st and 2nd axes of the both hand and wrist; the trapezium and trapezoid could not be differentiated.

The patient presented in this case report, denied that any other family member of her paternal side has upper limb morphological abnormalities or known cardiac defects. But her maternal grandfather and one of her maternal uncle has similar type of upper limb diformity but no known cardiac defect (Pedigree: 1). Possibility is that, they may be still undiagnosed.

Maternal Pedigree:1

Clinically all patients with HOS have upper limb anomalies⁶ and 85-95% have cardiac malformations.⁵ Lower limb abnormalities have not been reported. The clinical diagnostic criteria of HOS are personal and/or family history of cardiac septation and/or conduction defects in the setting of preaxial radial ray axis deformity.⁹ As stated above, the majority of patients also have cardiac malformations^{5,8} and almost every type of cardiac anomaly has been reported, either singly or as part of a group of multiple defects.⁵ The most common are ASD and ventricular septal defect (VSD), which vary in number, size and location.^{2,8} The most common ASD is of the secundum type;^{2,5} VSDs are usually located in the muscular trabeculated septum.⁸ Rhythm abnormalities sometimes accompany the morphological abnormalities,⁸ including atrioventricular (AV) block with bradycardia, atrial fibrillation and sudden death from heart block.^{5,8}

Our patient had the most common type of cardiac defect, ostium secundum type ASD. Patient's 12 lead ECG showed first degree AV block.

As a congenital disease, HOS is present at birth in all patients, although abnormalities may not be clinically apparent until later in life, when cardiac symptoms occur or when a child of the family has a more severe presentation. Cardiac conduction disease tends to progress with age, middle-aged individuals often presenting with significant AV block or atrial fibrillation.¹⁰

Chest X-ray may show enlarged pulmonary arteries due to pulmonary hypertension or cardiomegaly and evidence of congestive heart failure may be present. The echocardiogram is the procedure of choice to detect

morphological abnormalities of the heart. Apart from the common ASD and VSD, other cardiac anomalies may include abnormal isomerism and anomalous pulmonary venous return. ECG or 24-hour Holter recording may be valuable in the diagnosis and follow-up of rhythm abnormalities.

HOS is a rare disorder and little is known about its prognosis. Current evidence shows that prognosis depends on the severity of the cardiac manifestations. Patients with severe morphological or electrical cardiac manifestations have worse prognosis and may need surgery, device implantation or specific therapy. In cases of mild cardiac manifestations, patients may have a close to normal life expectancy.

Although our patient had morphological limb abnormalities and cardiac manifestations, these did not prevent her from leading a normal life.

Conclusion

We describe the case of a patient with a rare syndrome which went undiagnosed until late in life. Although she had manifestations from birth of both upper limb and cardiac disorders, a link between these two disorders was not established until later in life. She needs surgical closer of ASD and if she develop third-degree AV block then pacemaker implantation may be needed until then, she has to be followed by a cardiologist and a general practitioner.

Ethical disclosures

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent

The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Corrigendum

Evaluation of High Density Lipoprotein Cholesterol Concentrations among Elderly Ischaemic Stroke Patients.

Vol.-13, No.-1, January 2017, Page-8

Some printing mistakes were detected after printing the article.

A total 200 patients suffering from ischaemic stroke within the range of 61-95 years of age of both sexes with TIA, and hemorrhagic stroke were included, Patient with stroke after one month of onset, cases with anti-lipid drugs were excluded corrected.

Corrected-

A total 200 patients suffering from ischaemic stroke within the range of 61-95 years of age of both sexes were included. Patient with TIA, hemorrhagic stroke and stroke after one month of onset, cases with anti-lipid drugs were excluded.

Corrigendum

The Effect of Preoperative Pulmonary Arterial Hypertension on Incidence of Postoperative Atrial Fibrillation after Surgical Closure of Arterial Septal Defec (Secundum)

Vol.-13, No.-1, January 2017, Page-17

Some printing mistakes were detected after printing the article.

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Corrected-

Md. Asharaful Islam, AKM Manzurul Alam, Istiaq Ahmed, Manzil Ahmed, Mamun Hossain, Mizanur Rahman, Mohashin Reza