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Case Report

A Child with Holt-Oram Syndrome: A Case Report

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Abstract

Introduction and Importance: Holt-Oram syndrome (HOS), is a rare dominant autosomal disorder of TBX5 gene, characterized by morphological abnormalities of the upper limbs occurring in association with abnormalities of the heart, and by then, all patients with this syndrome should be sent to genetic investigation and counseling to determine other family members at risk.

Case Presentation: We report a case of a 5-years-old boy to normal family, presenting with morphological and cardiac malformation which were indicators for Holt-Oram syndrome, therefore the diagnosis was confirmed by genetic consultation. The patient underwent successful surgical repair for the skeletal and cardiac malformation, completed uneventfully.

Clinical Discussion: Holt-oram syndrome is a rare congenital disorder with unknown causes. Most cases occur spontaneously.

Although autosomal dominate mode of inheritance has been reported, HOS maybe present in patient with normal family because of a new mutation. Our patient was born to non-consanguineous healthy parents, with four healthy sibling and he was the only member of his family had the presentations.

The diagnosis was confirmed by clinical presentation and genetic consultation, so he had holt-oram syndrome with a new mutation.

The patient underwent successful surgical repair, completed uneventfully.

Conclusion: HOS is a rare syndrome can maybe present in patient with normal family. Many anomalies of this syndrome can be cured by surgery and supportive treatments, so they should be sent to genetic counseling for the early diagnosis and to determine other family members at risk.

Keywords: *Holt-Oram Syndrome; Hand-Heart Syndrome; T-BOX; ASD*

Abbreviations

CHD: Congenital Heart Disease; TAPVC: Total Anomalous Pulmonary Venous Connection; PHT: Pulmonary Hypertension; EF: Ejection Fraction; TTE: Transthoracic Echocardiography; ECG: Electrocardiogram; PVC: Pulmonary Venous Confluence; LA: Left Atrium

Introduction

Holt-Oram syndrome (HOS), also known as hand-heart syndrome [1,2], is a rare genetic disorder clinically characterized by morphological abnormalities of the upper limbs and congenital cardiac defects. Diagnostic criteria are abnormal skeletal, heart malformation or conduction disease and family history [7,8,11]. This syndrome was defined for the first time in 1960 [3], and with frequency of 0.7:100,000 [4-6,9]. This syndrome is caused by a TBX5 heterozygous mutation localized in the long arm of chromosome 12 (12q24.1). Forty percent of the cases occur due to new mutations, and the remaining cases occur due to familial inheritance [1]. TBX5 proteins are members of a conserved family of transcription factors that share a common DNA-binding domain called the T-box [8]. This transcriptional factor is associated with heart and limb development [9]. TBX5 is expressed in the epicardium, myocardium, and endocardium of embryonic and adult hearts [10]. In early cardiac development, this transcriptional factor activates genes associated with morphological septation and cardiomyocytes' maturation; later it is involved in the development of the cardiac conduction system [11].

The main clinical characteristics are: upper-limb malformation such as thumb aplasia, cardiac conduction disease. All patients present with limb anomaly and 75% of patients with HOS have a structural cardiac anomaly, isolated septal defects, usually (ASD) or ventricular septal defects (VSD), being the most common. Approximately 25% of patients have complex CHD [1,10,12].

Herein, we present a case of a 5-year-old boy with HOS Syndrome. He underwent a surgical repair of atrial septal defect which is the most common. We are reporting this case because it is a very rare condition and to highlight the importance of early diagnosis, to prevent the complications and to determine other risk of family members. Ethical approval for this study was obtained from ethics committee at Damascus University.

Work reported was done in Damascus university Hospital, and surgery was performed by a surgeon who had experience of 15 years in pediatric cardiac surgery. He worked as a professor and head of the department of cardiac surgery department. The work reported is in line with the SCARE 2020 criteria [13].

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Case Presentation

A 5-years-male presented to the pediatric clinic with a previous history of morphological defects of both upper limbs since birth.

The family history was normal, he was born to non-consanguineous healthy parents, and had four healthy sibling, natal and pre-natal history were negative with normal birth without complications. After the birth the skeletal malformations were noticed, then the baby was discharged with his mom.

Two months ago, the mother visited the pediatric clinic to determine the possibility of repairing the skeletal malformations and looking for the repetitive possibility in the next pregnancies.

In the clinical examination, the patient had thumb aplasia on the right side (Figure 1) and incomplete growth of the sternum (Figure 2). The patient was reported of having a low heart rate, around 70 bpm, but was always asymptomatic. The radiographic imaging of the hands showed a delayed bone age. During the physical examination, unnatural heart voice was heard, so he was referred to a cardiologist who was assessed the child and atrial septal defect type ostium secundum (ASD) 25 × 30 mm was diagnosed, and pulmonary hypertension that worsened at the time of diagnosis.

Figure 1: *Absence of the thumb of the right hand.*

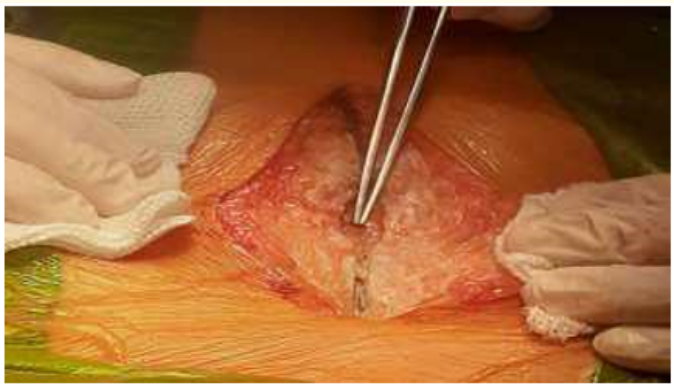

Figure 2: *Absence of the sternum.*

The genetic counselling and the clinical presentation showed that the diagnosis is Holt Oram Syndrome. The patient underwent surgical repair of the ASD, and after cardiopulmonary bypass, cardioplegia and cooling, an elective total surgical repair was done successfully. After the surgery, the infant was admitted to the pediatric cardiac intensive care unit. Hours later, the child general condition improved and was extubated. Next day, the patient's condition was stable. Four days after post-operative the patient was discharged from the hospital.

Discussion and Conclusion

HOS is one of the rare congenital abnormalities, inherited in an autosomal dominant and occurs in 1% to 2 - 3% of newborns, with frequency of 0.7: 100,000 [5,6,9] (if minor defects are included).

The incidence of CHD in HOS is high (75%) [1,2]. This syndrome is caused by a TBX5 heterozygous mutation localized in the long arm of chromosome 12 (12q24.1). Forty percent of the cases occur due to new mutations, and the remaining cases occur due to familial inheritance [1]. TBX5 proteins are members of a conserved family of transcription factors that share a common DNA-binding domain called the T-box [8].

In 15% of cases the patient has un-affected parent. The family history may be negative for HOS, but it may be apparently negative because of failure to recognize the signs and symptoms of HOS, early death of a person before the onset of symptoms, and mild phenotype with late onset of symptoms [9,12]. This is the same in our case, the parents and other members of the family are normal, which suggested a new mutation [10,11].

This transcriptional factor is associated with heart and limb development [9]. TBX5 is expressed in the epicardium, myocardium, and endocardium of embryonic and adult hearts [10]. In early cardiac development, this transcriptional factor activates genes associated with morphological septation and cardiomyocytes' maturation; later it is involved in the development of the cardiac conduction system [11]. The most common congenital heart defects are the ostium secundum type atrial septal defects and ventricular septal defects. However, more severe cardiac defects, such as Tetralogy of Fallot or a hypoplastic left heart, have been documented [4,6,7]. In complex CHD the mortality remained high, despite the progresses of cardiac surgery.

The genetic tests are recommended to all first-degree relatives if the mutation is known in probed, otherwise the tests like ECG, TTE and wrist radiograph are recommended for the screening of clinical changes, but we cannot perform the genetic test because this investigation is not available in our country.

Poster-anterior wrist radiograph is very important because the carpal bones abnormalities are present in 100% of the cases and sometimes are the unique sign of this disorder [4-6].

HOS is an autosomal dominant condition, being caused by a mutation in TBX5 gene [11,12]. TBX5 which expressed especially in the heart and upper limb, but also in lungs and eyes [1,7,11]. The gene expression of TBX5 is different across the heart tube [2-4], so an early diagnosis is necessary for preventing complications, and they should be sent to genetic counseling for identifying other family members at risk.

Provenance and Peer Review

Not commissioned, externally peer reviewed.

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