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Upper Limb Anomalies and Cardiac Defects: Presentation of Holt-Oram Syndrome and its Relevance to Pediatric Providers

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Abstract

Holt-Oram Syndrome (HOS) is the most common of the heart-hand syndromes. The syndrome is characterized by limb deformities in conjunction with structural cardiac defects, and oftentimes conduction abnormalities. The cardiac defects can range from septal defects to more severe cardiac defects including tetralogy of Fallot, double outlet right ventricle, valvular atresia, and truncus arteriosus. HOS most commonly occurs de novo, but can also be inherited in an autosomal dominant manner. Diagnosis can be confirmed by molecular genetic testing that identifies the pathogenic variant on the q arm of chromosome 12, TBX5. Patients with HOS require close cardiac surveillance and follow-up with an orthopedic center. This article will discuss HOS, the differential diagnosis, and recommendations for continuation of care for these at-risk patients.

Keywords: Holt-Oram Syndrome; Cardiac defects; Heart-hand syndromes; Abnormalities

Abbreviations: HOS: Holt-Oram Syndrome; VSD: Ventricular Septal Defect; ASD: Atrial Septal Defect.

Introduction

We describe a case of a full term female infant with upper limb and cardiac septation anomalies. Physical exam and further workup revealed multiple septal defects, consistent with Holt-Oram Syndrome (HOS). HOS is an important entity to recognize due to the significant cardiac defects and their potential sequelae. We present a brief review of the disease and key concepts to take away. HOS was first described by Mary Holt and Samuel Oram as a collection of clinical characteristics: upper limb malformations and cardiac defects [1]. The limb deformities can be unilateral, bilateral, and symmetric or asymmetric. Some defects are very subtle, including abnormal forearm pronation and supination, or restricted shoulder joint movement. Structural cardiac defects most commonly involve the septum as in the case of ventricular septal defect (VSD) or atrial septal defect (ASD). Conduction disturbances are present in many HOS patients regardless of whether they have perceived structural cardiac anomalies. Patients may present with sinus bradycardia or first degree atrioventricular block at birth, but it is known to progress unpredictably to second or even third degree heart block, with and without atrial fibrillation.

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HOS usually occurs in de novo cases, however can also be inherited in an autosomal dominant manner that may or may not show genetic anticipation [2,3]. Population-based studies have suggested that the prevalence of HOS is about 1 in 100,000. A 20 year study covering 30% of Europe's annual birth population determined that a large number of HOS patients (about 25%) have severe congenital heart disease such as tetralogy of Fallot, double outlet right ventricle, valvular atresia, and truncus arteriosus [4]; for these reasons it is important for pediatric providers to be aware of HOS.

Case Presentation

The patient was born at 36 weeks gestation via an uncomplicated cesarean section secondary to suspected limb anomalies discovered on second trimester ultrasound. The mother was a 26 year old primigravid mother with a history of ASD and HOS and negative serologies. Her only medication was a prenatal vitamin. Family history was remarkable for HOS in the mother, maternal aunt, maternal uncle, and maternal grandmother.

The baby did well following delivery with no circulatory abnormalities, increased work of breathing, or other issues. She remained on the well-baby service. Examination revealed an active precordium with a 2/6 holosystolic murmur best heard on the left midsternal border, as well as abnormally shaped clavicles, absent thumbs and absent radii. She was macrocephalic with cranial molding.

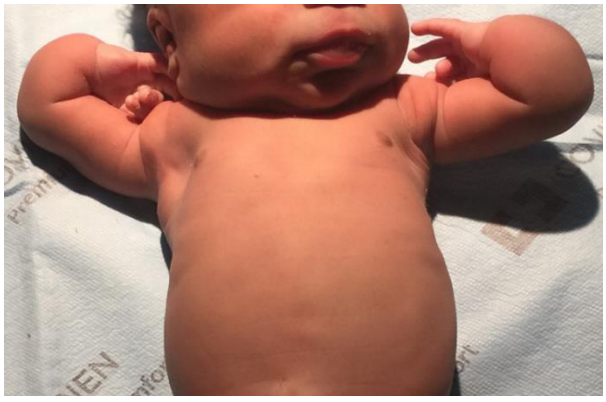

Figure 1: Patient with Holt-Oram Syndrome and absent radii with truncated and shortened forearms.

There were no abnormal facies, anterior fontanelle was open, soft, and flat, nares patent, lungs clear to auscultation bilaterally, and abdomen soft without masses or hepatomegaly, normal 3-vessel cord, patent anus, normal external female genitalia, and skin was warm and dry with no rashes. An echocardiogram performed on the first day of life was significant for multiple apical muscular VSDs in "Swiss cheese formation," a patent foramen ovale versus small secundum ASD with bidirectional shunting, and a tiny patent ductus arteriosus with left to right shunting. Electrocardiogram was normal for age.

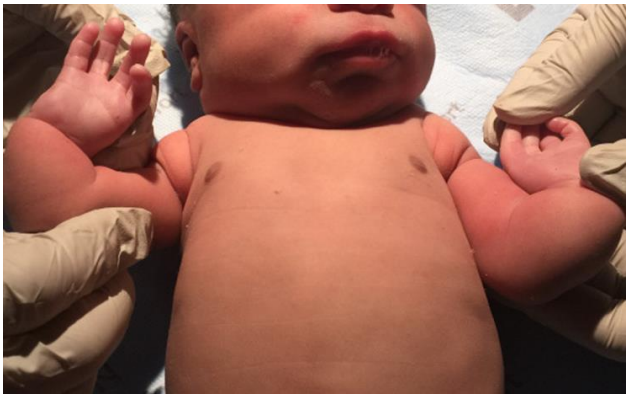

Figure 2: Same patient with absence of thumbs bilaterally.

Discussion

The diagnosis of HOS is generally made based on several criteria and is the most common of the heart-hand syndromes [5]. For clinical diagnosis, a patient must have a preaxial radial ray anomaly, as well as either personal or family history of congenital heart malformation (especially those occurring in the muscular septum) and/or conduction defects. Or, the diagnosis can be made via molecular genetic testing that identifies a pathogenic variant in a gene found on the q arm of chromosome 12, TBX5. The TBX5 gene is involved in most cases, and it is known that more than 70% of patients who fulfill the strict clinical diagnostic criteria have a pathogenic variant identified in TBX5 6]. Sequence analysis of TBX5 is typically performed first, and if no pathogenic variant is found, gene-targeted deletion/duplication analysis can be done.

It is important to note the lack of prenatal diagnosis for our patient. Fortunately for her, the cardiac disease was not hemodynamically significant. Most cardiac anomalies are clearly visible by 18-20 weeks of gestation, and the radius and ulna are able to be visualized even earlier. However even in population-based studies, prenatal detection rates did not improve over time, despite the fact that they could have been visualized on prenatal ultrasound [4].

While patients with HOS have been noted to have simultaneous anomalies in other organ systems [4], alternate diagnoses (Table 1) should be considered if there are malformations noted in the kidneys, vertebra, craniofacies, auditory system, lower limbs, anus or eyes.

Inheritance mode	Diagnosis
Autosomal dominant	• Duane-radial ray syndrome • Ulnar-mammary syndrome • Townes-Brocks syndrome • Heart-hand syndrome II • Heart-hand syndrome III
Autosomal recessive	• Fanconi Anemia • Thrombocytopenia-absent radius syndrome
Chromosomal	• 22q11.2 deletion
Other	• Teratogenic embryopathies (valproate, thalidomide) • VACTERL

Table 1: Differential Diagnosis of Holt-Oram Syndrome.

The TBX5 gene is the only gene implicated in HOS; it is localized to 12q24.21. Most of the mutations are nonsense and frame shift pathogenic variants that lead to truncated TBX5 mRNAs that are degraded, resulting in haploinsufficiency. It has been reported that pathogenic missense variants at the 5' end of the T-box are associated with more serious cardiac defects, while missense variants at the 3' end of the T-box result in more pronounced limb defects. All affected individuals have an abnormal carpal bone, and it is notable that left upper extremities are affected more frequently than right [6]. HOS is thought to be mainly a de novo process, with about 15% of cases familial and 85% sporadic. While there are clinical reports showing higher familial inheritance, ascertainment bias is important to consider as a confounding factor. Interestingly, there are conflicting reports of the rate of severe CHD in patients with HOS, ranging from 17% [7] to 25% [4].

The most important aspect of managing patients with HOS is close cardiac surveillance. All patients with HOS need to be followed by a cardiologist. As conduction defects can progress rapidly to life-threatening, all patients should have annual EKG at the minimum, with more frequent and detailed follow up depending on their personal degree of cardiac involvement. For example, those with septal defects should also undergo regular echocardiograms. Treatment of cardiac disease is dependent on the specific disease. In the treatment of limb anomalies, patients should be assessed by orthopedic specialists, with corrective surgery and aggressive physical and/or occupational therapy to achieve the best possible functional outcome. If limb involvement is not grossly obvious, radiographs can be done to determine if subtle anomalies of the carpal bones are present. Genetic counseling is an important part of management as well. Prenatal counseling includes identification of the presence of the pathogenic variant followed by detailed ultrasound evaluation [6]. It should be noted that patients with HOS have no known risk of intellectual impairment. Moreover, despite smaller familial case series that may point to the contrary, examination of larger, multigenerational kindreds with HOS does not support the presence of genetic anticipation [2,3]. The risk to siblings is 50% if a parent is affected with the TBX5 pathogenic variant. If not, risk is similar to that of the general population [6].

Our patient has been followed closely since birth. The ASD, PDA, and VSDs closed spontaneously. She continues occupational therapy for limb use and has not had undergone any surgical intervention for her limbs. She has had normal growth. Social and language development are appropriate and our patient participates in gymnastics. She is followed annually by cardiology and with cardiac exams and EKG. Last EKG demonstrated borderline prolonged PR but no other abnormalities. She is cleared for all activities.

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