

Holt-Oram syndrome

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[Abstract](#)
[Keywords](#)
[Disease name and synonyms](#)
[Definition](#)
[Incidence](#)
[Etiology](#)
[Clinical description](#)
[Prenatal diagnosis](#)
[Genetic counseling](#)
[Management](#)
[References](#)

Abstract

Holt-Oram syndrome (HOS) is characterized by mild-to-severe congenital cardiac defects and skeletal abnormalities of the upper limbs. The most common cardiac disorder is an ostium secundum atrial septal defect (ASD), followed by ventricular septal defect (VSD) and ostium primum ASD. Electrocardiographical abnormalities such as various degrees of atrioventricular block have also been reported. In addition hypoplastic peripheral vessels of the upper limbs have been observed. Frequent orthopedic signs are radial ray abnormalities, absent or abnormal radius, upper limb-transverse elements missing and various thumb anomalies. One out of 100,000 live births is affected. More than 300 cases have been published, revealing a wide spectrum of clinical signs. HOS is an autosomal dominant disorder with complete penetrance. The underlying genetic defect was found on the long arm of chromosome 12 (12q2). Mutations in the TBX3 and TBX5 genes lead to a wide range of phenotypes. Echocardiography can be used to detect cardiac anomalies in the offspring of a parent with HOS. Genetic counseling is recommended. Surgical operation can be performed in order to treat ASD.

Keywords

Holt-Oram syndrome - congenital heart defects - septal defects limb anomalies.

Disease name and synonyms

Holt-Oram syndrome (HOS)
 Atriodigital dysplasia
 Heart-hand syndrome (1)

Definition

The syndrome was first reported in 1960 by Mary Clayton Holt and Samuel Oram, who detected an atrial septal defect (ASD) in members of 4 generations of a family. ASD was associated with "a congenital anomaly of the thumbs which lay in the same plane as the fingers, their terminal phalanges being curved

inwards" (2). They described the triad of ASD, conduction disturbances and hand malformations.

Incidence

One out of 100,000 live births is affected (3). More than 300 cases have been published, revealing a wide spectrum of clinical signs.

Etiology

HOS is an autosomal dominant disorder with complete penetrance. The underlying genetic defect was found on the long arm of chromosome 12 (12q2). Mutations in the *TBX3* and *TBX5* genes lead to a wide range of phenotypes typical of HOS. These genes play an

important role in cardiac and skeletal development (3, 4). Mutations in these two T-box genes on chromosome 12q2 give an embryologic basis for the prevalence of ASD, ventricular septal defect (VSD) and left-sided malformations observed in patients with HOS (5).

Clinical description

Orthopedic signs

The review of orthopedic literature remains poor (6). Amputation of rudimentary or hypoplastic fingers was reported. Frequent signs are radial ray abnormalities, absent or abnormal radius, upper limb-transverse elements missing and various thumb anomalies. Occasional signs are scoliosis, abnormal ribs, hypertelorism, scapula anomaly and pectus excavatum. Syndactyly of toes or fingers and radio-ulnar synostosis are rarely reported.

Cardiological signs

Arrhythmia

In their first paper Holt and Oram described "bizarre atrial arrhythmias". Since then, various types of arrhythmias have been reported (table 1).

Most of the patients who presented with arrhythmias had anatomical heart anomalies as well (3). Thirty-nine percent of the patients with HOS showed no anatomical heart anomalies but only ECG abnormalities (7). However, cardiac involvement may be absent. Permanent cardiac pacemaker implantation is sometimes required in patients with HOS.

Table 1: ECG abnormalities in patients with HOS

ECG abnormality	Reference
Sinus arrest	8
Various degrees of atrioventricular block	9
Right bundle branch block	10
Sinus node dysfunction	1
Wandering pacemaker	1
Bradycardia	1
Atrial fibrillation / flutter	1
Supraventricular tachycardia and Wolf-Parkinson-White syndrome	11
Premature ventricular complexes	1

Congenital heart defects

Although a secundum ASD is most common in 60 % of the patients with HOS (12), a wide variety of other anatomical abnormalities with more complex congenital malformations have been reported to occur in up to 18 % of the patients (12). The next common defect is a ventricular septal defect. Those septal defects were frequently observed. Intrafamilial variability of cardiac spectrum was noted. Three patients exhibiting a different type of ASD were reported by Cachat (13). The severity of the cardiac spectrum is not always proportional to that of the

upper limb deformity. Table 2 demonstrates the cardiac anatomical anomalies in patients with HOS.

Table 2: Cardiac anatomical anomalies in patients with HOS

Cardiac anatomical anomalies	Reference
Ostium primum ASD	1
Ostium secundum ASD	14
VSD	15
VSD and infundibular pulmonary stenosis	16
Complete atrioventricular canal defect	16
Mitral valve prolapse	17
Hypoplastic left heart syndrome	16,18
Coarction of aorta	19
Patent ductus arteriosus	6,19
Subaortic stenosis	16
Pulmonary hypertension	19,20
Endocardial cushion defect	21
Tetralogy of Fallot	10,22
Single ventricle	10
Hypoplastic pulmonary artery	23
Double outlet right ventricle with mitral valve atresia	16
Tricuspid atresia and anomalous return of pulmonary vein into the right atrium	24
Persistent left superior vena cava	16,25
Truncus arteriosus	26
Cardiomyopathy	27

Anomalies of the (great) vessels

It is important to know that hypoplastic peripheral vessels of the upper limbs have not been frequently observed (1, 28), since this might lead to difficulties in cardiac catheterization. Anomalies of vena cava (25,29), subclavian artery (30), coronary arteries (30) and other great vessels (16,30) like coarction and hypoplastic aortic arch have been described.

Prenatal diagnosis

Echocardiography can be used to detect cardiac anomalies in the offspring of a parent with HOS (33).

Genetic counseling

Genetic counseling is recommended.

Management

Operation of 4 patients was reported by Rainer *et al.* (31) in order to treat ASD. Solit *et al.* (25) reported operation of one case (ASD closure) with supraventricular tachycardia in the postoperative course. Incidence of postoperative arrhythmias may be higher after ASD closure in patients with HOS compared to other patients with ASD closure (32). This may be related to the underlying chromosomal abnormality, the operative technique or even both.

In summary the cardiac spectrum of HOS is important for prognosis. In patients affected with ASD alone, prognosis after surgical or interventional repair is excellent.

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