Case Report

Holt-Oram syndrome

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ABSTRACT
Holt-Oram syndrome with its many synonyms is an autosomal dominantly inherited disorder that causes abnormalities of the upper limbs and heart. Holt and Oram first described this condition in 1960 in a family with atrial septal defects (ASD) and thumb abnormalities and no more than about 350 cases of this rare condition have been reported worldwide. We report a case here with multiple anomalies. (Rawal Med J 2005;30:38-40).

KEY WORDS: Holt Oram Syndrome, Atriiodigital Dysplasia, Cardiac-Limb Syndrome, Pseudothalidomide syndrome, Heart-Hand Syndrome (Holt-Oram Type), ASD, VSD.

CASE REPORT
A 14 year old Afghan refugee girl was referred from a private clinic for consultation. She was complaining of dyspnea and palpitations. On physical examination she was not very dyspneic at rest but had central cyanosis, had a pulse of 110 beats per minute with no pauses or irregularity, and was bounding. She had no clubbing. Her blood pressure was 120/70 mm Hg and normal JVP. A left parasternal ventricular thrill was palpable and a systolic murmur was heard throughout the precordium and on the right side of the chest but was not radiating to the axillae. There was a systolic murmur at the pulmonary area also. Due to tachycardia the split of S2 could not be heard neither could be the singularity of the S2 appreciated.

The patient had hypoplastic thumbs and had difficulty of pronation and supination of the hands. The thumb was “digitalized” i.e.finger like (Figure 1).
Radiography of the wrist revealed hypoplasia of the thumbs and carpal bones. The metacarpal of thumb was rudimentary on the right side (Figure 2).
Figure 3. Apical view showing VSD and overriding aorta.
She was clinically diagnosed as Holt-Oram syndrome with hypoplastic thumbs and difficulty of pronation and supination probably due to deformities of radioulnar joints. The cardiac abnormalities were diagnosed as a VSD with an ASD with probable pulmonary stenosis.

Her ECG showed right ventricular hypertrophy with a right bundle branch pattern. There were no other conduction abnormalities. The chest radiograph showed cardiomegaly without any skeletal abnormalities. Echocardiography was done which showed an overriding aorta and pulmonary stenosis, confirming the diagnosis of Pentalogy of Fallot (Figure 3). Interestingly, the patient had survived without many complications without an associated patent ductus, till this age.

**DISCUSSION**

Holt-Oram syndrome, also called heart-hand syndrome, is an inherited disorder that causes abnormalities of the upper limbs and heart. Holt and Oram first described this condition in 1960 in a 4-generation family with ASD and thumb abnormalities.\(^1\) Cardiac symptoms depend on the type of congenital heart defect. ASD, the most common heart defect, causes no symptoms in the majority and may be detected only when limb deformities are observed. Interestingly, only the upper limbs are affected. This is because of a defect in a genetic sequence which codes for the heart and the upper limbs both.\(^2\)

Although bilateral, the left side is affected more significantly. Abnormalities may be unilateral or bilateral and asymmetric and may involve the radial, carpal, and thenar bones. Aplasia, hypoplasia, fusion, or anomalous development of these bones produces a spectrum of phenotypes, including triphalangeal or absent thumbs. Occasionally, upper limb malformation can be sufficiently severe to produce phocomelia (a malformation in which the hands are attached close to the body); this has been termed Pseudothalidomide syndrome.

In the heart, the commonest lesion is a secundum type of ASD. Other anomalies include ventriculoseptal defect (VSD), atrioventricular (AV) block, pulmonic stenosis (including peripheral arterial), and mitral valve prolapse. Sometimes, more complex anomalies\(^3\)\(^4\)\(^5\) may be present like tetralogy of Fallot, truncus arteriosis, hypoplastic left heart and endocardial cushion defects. In one study, malformation of the renal and cerebral arteries has also been described\(^6\). Arrhythmias are also common in Holt Oram syndrome and include first degree heart block, wandering atrial pacemaker, atrial ectopics, AV nodal block, right bundle branch block and sinus bradycardia, syncope, sinus arrest and even sudden death can occur. Ventricular ectopics and tachycardia are almost nonexistent in
A scoring system to assess severity has been recommended \(^7,8\) and later modified\(^9\) (Table 1).

**Table 1. Scoring System to Assess in Holt-Oram Syndrome**

**Skeletal Abnormalities**

0 No abnormality on physical or radiological examination

1 Minor abnormalities, including reduced thenar eminence, clinodactyly, or hypoplasia of the thumb

2 Triphalangeal or aplastic thumbs, radial/ulnar hypoplasia

3 Arms and forearms present, but with bone(s) missing

4 Phocomelia

**Cardiac Abnormalities**

0 Asymptomatic, with no abnormal physical findings

1 Innocent murmur or conduction defect

2 Structural heart abnormality not requiring surgery

3 Structural heart abnormality requiring surgery, but not life threatening

4 Potentially lethal malformation

Imaging studies of upper limbs may reveal the different types of anomalies like small glenoid fossa, abnormalities at the acromial region, hypoplastic humerus and phocomelia. Radioulnar or Humeralular synostosis may be present. Radial hypoplasia or absence, and ulnar absence are all reported. In the carpal bones there may be duplication, hypoplasia, fusion or irregularity. There may be additional carpal bones.

Chest radiography may be completely normal or reveal the type of cardiac anomaly. Cardiomegaly is frequent.
Doppler-echocardiography (ECHO) evaluation identifies the primary heart defect, its severity, and associated cardiac malformations. Magnetic resonance imaging (MRI) is helpful for delineating cardiac and skeletal involvement. Karyotyping and molecular studies may be needed to know the chromosomal abnormalities. Prenatal diagnosis is possible by the chromosomal studies of the chorionic villous sampled.

A physician should establish the complete diagnosis and counsel the patient and parents and then refer the patient to the cardiologist and cardiac surgeon. Surgical correction of both skeletal and cardiac abnormality depends upon the anomaly and may be completely or partially correctable depending upon the anomaly and age of the patient.

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REFERENCES