Familial Heart Disease with Skeletal Malformations- Holt – Oram Syndrome

Karim Al-naffi

It is well known that congenital heart disease and skeletal deformities occur together in several clinical syndromes such as 13-15 or DI trisomy, 16-18 or EI trisomy, mongolism, XO syndrome, XXXX, XXXY, Ellis Van Crevald syndrome and Marfan syndrome yet there are a lot of skeletal deformities which is associated with congenital heart disease, so if found such deformities we should examine the heart of these patients for congenital anomalies.

Below is a case report of a family having one of these conditions namely Holt Oram Syndrome, with review of this hereditary disease, and a list of her diseases which have skeletal anomalies and congenital heart disease.

Case report

Q R is 27 yr old patient presented with cough & dyspnea after upper respiratory tract infection. He is a member of a family of five brothers & one sister, his father is the son of his mother aunt O/E. He is orthopoenic, not cyanosed, B.P100/60. Respiratory rate 30/min. JVP 5cm above costal margin.

He has skeletal deformities which include; small atrophied left upper limb with the absence of the arm with the hand attached to the forearm, he hand which is small, the fingers shows parallel fingers including the thumb which lost apposition to the other finger in addition, the syndactsy of the fingers. As seen in picture number 1., the right upper limb also is deformed with loss of the thumb, the chest is asymmetrical the right one is more prominent.

His mother has also deformities in her hands only, where there is loss of the thumb apposition, she has ASD as well. One of his brothers have hand anomalies (loss of apposition of the thumb with mitral valve prolapsed), the other member of the family are normal.

Upper limbs and shoulders of the patients
Hand of the patient

Heart examination revealed apex beat in the sixth intercostals space, with visible pulsation at the pulmonary area, there is fixed splitted second heart sound in the pulmonary area with ejection systolic murmur grade 3. Also, there is long systolic murmur grade 2-3 at mitral area with radiation to the axilla.

Echocardiography shows big ASD (picture) with left to right flow, dilated both ventricles with diminished contractility, mitral valve prolapse, in addition, there was tricuspid regurgitation.

His ECG shows right axis deviation, partial RBBB & RVH.
Chest X-Ray revealed cardiomegaly

**Holt-Oram Syndrome (Heart-Hand Syndrome)**

The Holt-Oram syndrome (Mendelian Inheritance) also called the heart-hand syndrome, is an inherited disorder that causes congenital heart abnormalities and skeletal malformations of the upper limb, ranging from subtle changes, such as hypoplasia or absence of the thumb, to frank phocomelia, with the left side usually being more severely affected.

**Synonyms:**

Atrio-extremital dysplasia, atriodigital dysplasia, cardiac limb syndrome, cardio-osseous syndrome, cardiomelic syndrome, digito-atrial dysplasia, dysplasia atriodigitalis, heart and hand syndrome, heart-upper-limb-syndrome, heart-hand syndrome, upper limb-cardiovascular syndrome.

Mary Holt was Samuel Oram's assistant from Cardiac Department, King's College Hospital when they, in 1960, described a familial condition in which atrial septal defects were associated with malformations of the thumb, forearm, bones and shoulder girdle in successive generations. In his account of the delineation of the syndrome Oram mentioned that as Holt was a lady, it seemed only proper to
him that her name should appear as first author on their paper! The syndrome is transmitted as an autosomal dominant trait. The syndrome is transmitted as an autosomal dominant trait that is highly penetrant, although the clinical manifestations vary and range from subclinical radiographic findings to overt, life-threatening disease.

The skeletal deformities are upper-limb anomalies are always present. These may be unilateral or bilateral and involve structures derived from the embryonic radial ray, typically the radial, carpal, and thenar bones. Aplasia, hypoplasia, fusion, and anomalous development of these structures produce a wide spectrum of phenotypes including triphalangeal or absent thumbs, foreshortened arms, and phocomelia.

The most common cardiac defects associated with HOS are ostium secundum atrial septum defect (in ~60% of the cases), followed by ostium primum atrial septum defect and ventricular septum defect (Sletten and Pierpont, 1996). However, a wide variety of complex cardiac anomalies may occur in HOS, such as mitral valve prolapse, tetralogy of Fallot, hypoplastic left heart syndrome and tricuspid atresia (Zhang et al., 1986; Glauser et al., 1989; Lehner et al., 1994; Bossert et al., 2002). These anomalies may be accompanied by a variety of supraventricular and ventricular electrocardiogram (ECG) abnormalities, consisting of conduction or pacemaker disturbances up to complex arrhythmia (Zhang et al., 1986). In addition, anatomical anomalies of the large vessels have been reported, including patent ductus arteriosus, hypoplastic pulmonary artery and persistent left superior vena cava (Massumi and Nutter, 1966; Solit et al., 1973). An aortopulmonary window (APW) is a rare cardiac malformation and was first described by Elliotson (1830). In 90% of patients, it consists of a large oval defect between the ascending aorta and the pulmonary trunk.

Disturbances of cardiac rhythm occur frequently in affected persons and include sinus bradycardia and variable degrees of atrioventricular block. Mutations in a gene on chromosome 12q2 can produce a wide range of disease phenotypes characteristic of the Holt-Oram syndrome. This gene has an important role in both skeletal and cardiac development.

References

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# FAMILIAL HEART DISEASE WITH SKELETAL MALFORMATIONS

**Table 1. Mendelian Gene Syndromes Associated with Congenital Heart Anomalies**

<table>
<thead>
<tr>
<th>Etiologic Syndrome</th>
<th>Frequency of Cardiac Anomalies</th>
<th>Distinguishing Features</th>
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<tbody>
<tr>
<td></td>
<td>All (%)</td>
<td>Distinctive or Most Common</td>
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<tr>
<td><strong>Autosomal Dominant</strong></td>
<td></td>
<td></td>
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<tr>
<td>Adams-Oliver syndrome</td>
<td>20</td>
<td>Left-sided obstruction (eg, COA, parachute MVP), TOF</td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>95</td>
<td>(P)PS, TOF/TOF with PA, ASD, VSD</td>
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<tr>
<td>Char syndrome</td>
<td>60</td>
<td>PDA</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
<td>25</td>
<td>VSD, ASD, PS, TOF</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>80</td>
<td>ASD± other CVM, VSD, TA, TOF, PAPVC, conduction defect</td>
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<tr>
<td>Neurofibromatosis</td>
<td>2</td>
<td>PSV, ASV, COA, HCM</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>85</td>
<td>PSV, ASD, AVSD partial, COA, HCM</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>35</td>
<td>PDA, ASD, VSD, left-sided obstruction (eg, COA, HLHS)</td>
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<tr>
<td>Williams syndrome</td>
<td>60</td>
<td>SVAS, PS, other left-sided obstructions (eg, ASV, MS, COA)</td>
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<tr>
<td><strong>Autosomal Recessive</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ellis-van Creveld syndrome</td>
<td>60</td>
<td>AVSD, common atrium, ASD primum</td>
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<tr>
<td>Fryns syndrome</td>
<td>50</td>
<td>ASD, VSD, conotruncal</td>
</tr>
<tr>
<td>Keutel syndrome</td>
<td>70</td>
<td>(P)PS</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>45</td>
<td>ASD, VSD, complete AVSD, TAPVC</td>
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<tr>
<td><strong>X-linked Recessive</strong></td>
<td></td>
<td></td>
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<tr>
<td>Simpson-Golabi-Behtel syndrome</td>
<td>25</td>
<td>ASD; VSD; rare, variable cardiomyopathy</td>
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<tr>
<td><strong>Suspected Gene Etiology</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cardio-facio-cutaneous syndrome</td>
<td>75</td>
<td>ASD, HCM</td>
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<tr>
<td>Hall-Hittner syndrome (CHARGE association)</td>
<td>80</td>
<td>Conotruncal/arch, assorted CMVs</td>
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<tr>
<td>Costello syndrome</td>
<td>60</td>
<td>MVP, AV, thickening HCM, arrhythmia (atrial tachycardia)</td>
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<tr>
<td>PHACES syndrome</td>
<td>100</td>
<td>COA; IAA, A right; double, cervical aortic arch</td>
</tr>
<tr>
<td>Ritscher-Schinzel syndrome (3C)</td>
<td>100</td>
<td>TOF, DORV, AVSD</td>
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ASD=atrial septal defect, ASV=aortic stenosis, va