CASE REPORT

Familial Heart Disease with Skeletal Malformations- Holt – Oram Syndrome

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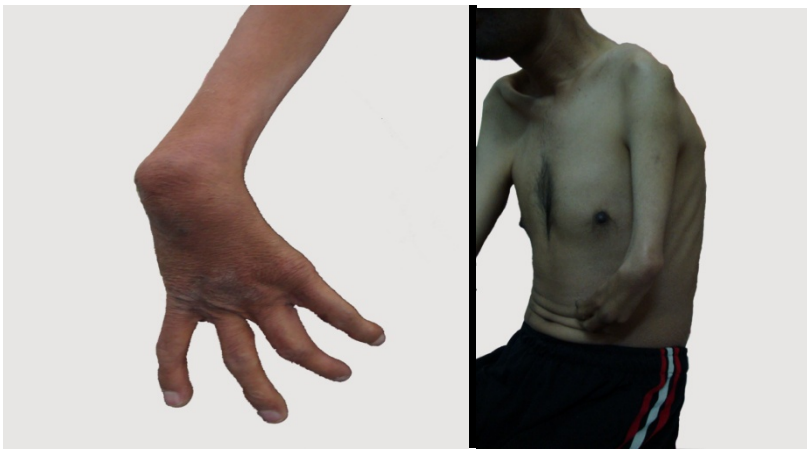
It is well known that congenital heart disease and skeletal deformities occur together in several clinical syndromes such as 13-15 or DI trisomy,16-18 or EI triosomy, mongolism, XO syndrome, XXXXX, XXXY, Ellis Van Crevald syndrome and Marfan syndrome yet there are a lot of skeletal deformities which 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 repot of a family having one of these condition 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

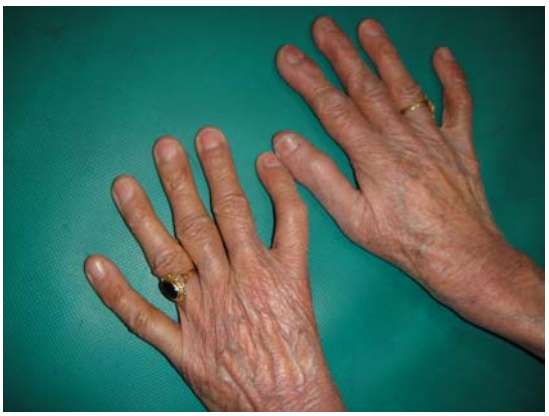
Q R is 27 yr old patient presented with cough & dyspnea after upper respiratory tract infection. He is a member of a family of five brothers & one sister, his father is the son of his mother aunt O/E.
He is orthopoenic, not cyanosed, B.P100/60. Respiratory rate 30/min. JVP 5cm above costal margin
He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

His mother has also deformities in her hands only, where the 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



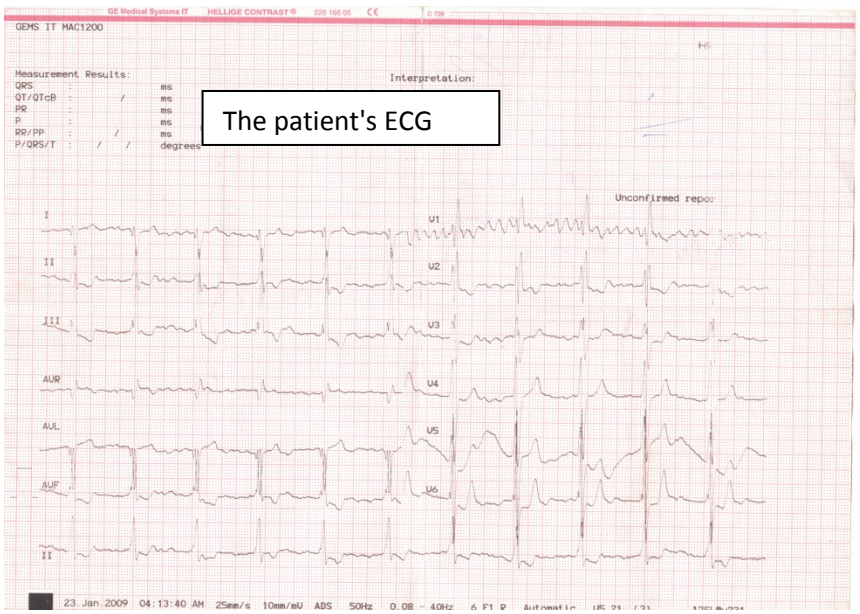
Upper limbs and shoulders of the patients

Hand of the patient

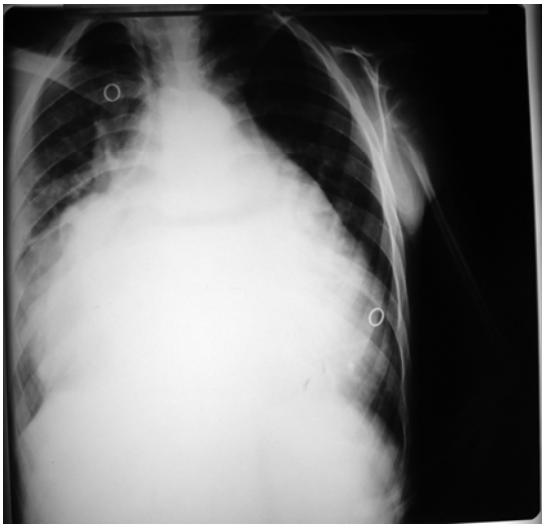


The hands of the patient's mother

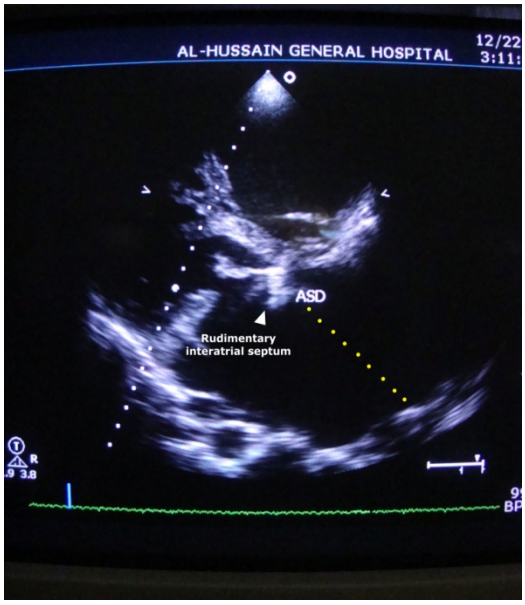
Heart examination revealed apex beat in the sixth intercostals space ,with visible pulsation at the pulmonary area, there is fixed splitted second heart sound in the pulmonary area with ejection systolic murmur grade 3,Also there is long systolic murmur grade 2-3 at mitral area with radiation to the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



. ECHO of the patient

Holt-Oram Syndrome (Heart-Hand Syndrome)

The Holt-Oram syndrome (Mendelian Inheritance) [(1)] 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 fromCardiac Department, King's College Hospitalwhen 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 t humbs, 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 aorto-pulmonary 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[2,3,4].

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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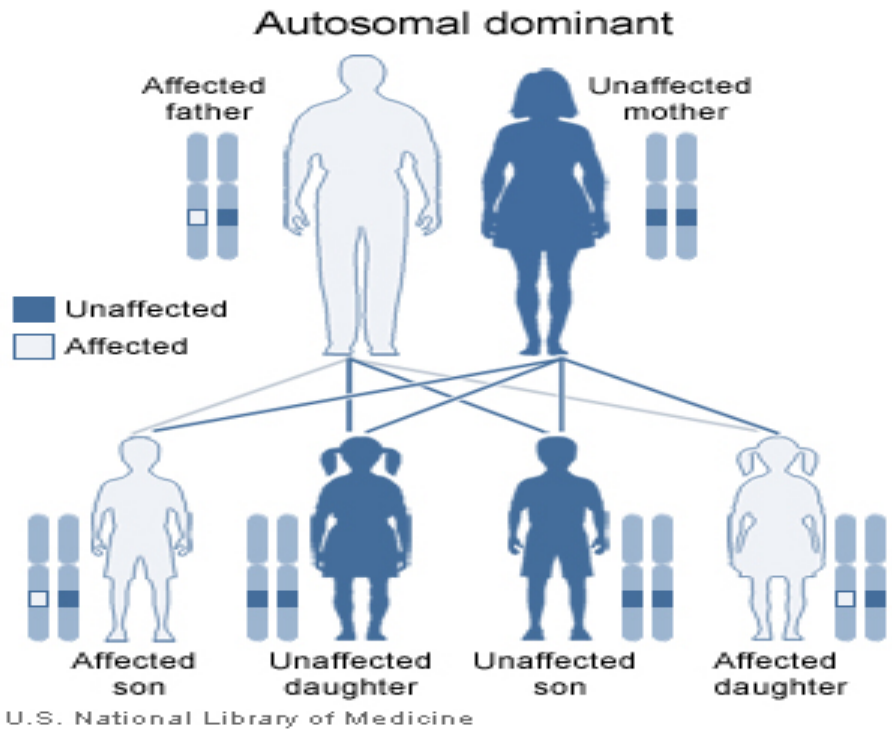
Autosomal dominant
Affected father
Unaffected mother
Unaffected
Affected
Affected son
Unaffected daughter
Unaffected son
Affected daughter
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FAMILIAL HEART DISEASE WITH SKELETAL MALFORMATIONS

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

Etiologic Syndrome	Frequency of Cardiac Anomalies†		Distinguishing Features
	All (%)	Distinctive or Most Common	
Autosomal Dominant			
Adams-Oliver syndrome	20	Left-sided obstruction (eg, COA, parachute MVP), TOF	Scalp cutis aplasia, terminal transverse limb defects
Alagille syndrome	95	(P)PS, TOF/TOF with PA, ASD, VSD	Bile duct paucity, chronic cholestasis, butterfly vertebrae, posterior embryotoxon
Char syndrome	60	PDA	Anomalies on fifth finger, supernumerary nipple
Cornelia de Lange syndrome	25	VSD, ASD, PS, TOF	Upper limb deficiency, GI anomalies
Holt-Oram syndrome	80	ASD± other CVM, VSD, TA, TOF, PAPVC, conduction defect	Upper limb malformations
Neurofibromatosis	2	PSV, ASV, COA, HCM	Café au lait macules, optic glioma, scoliosis, pseudarthrosis, neurofibromas
Noonan syndrome	85	PSV, ASD, AVSD partial, COA, HCM	Short, webbed neck; pectus deformity; cryptorchidism
Rubinstein-Taybi syndrome	35	PDA, ASD, VSD, left-sided obstruction (eg, COA, HLHS)	Broad thumbs and great toes
Williams syndrome	60	SVAS, PS, other left-sided obstructions (eg, ASV, MS, COA)	Hypercalcemia, hypodontia, hypoplastic nails
Autosomal Recessive			
Ellis-van Creveld syndrome	60	AVSD, common atrium, ASD primum	Short limbs, polydactyly, hypoplastic nails, dental anomalies
Fryns syndrome	50	ASD, VSD, conotruncal	Diaphragmatic hernia, distal digital hypoplasia
Keutel syndrome	70	(P)PS	Short digits, mixed hearing loss, cartilage calcification
Smith-Lemli-Opitz syndrome	45	ASD, VSD, complete AVSD, TAPVC	Two- to three-toe syndactyly, cleft palate, lung anomalies, genital anomalies
X-linked Recessive			
Simpson-Golabi-Behmel syndrome	25	ASD; VSD; rare, variable cardiomyopathy	Macrosomia, cleft palate, supernumerary nipples, hernias, hypospadias, poly/syndactyly
Suspected Gene Etiology			
Cardio-facio-cutaneous syndrome	75	ASD, HCM	Sparse, curly hair; low, rotated ears; hyperkeratosis
Hall-Hittner syndrome (CHARGE association)	80	Conotruncal/arch, assorted CVMs	Coloboma, choanal atresia, genital anomalies, ear anomalies
Costello syndrome	60	MVP, AV, thickening HCM, arrhythmia (atrial tachycardia)	Skin/joint laxity, fine/curly hair, deep palm creases, ulnar deviation, papillomata
PHACES syndrome	100	COA; IAA, A right; double, cervical aortic arch	Posterior fossa malformations, hemangiomas, eye anomalies
Ritscher-Schinzel syndrome (3C)	100	TOF, DORV, AVSD	Posterior fossa malformations, cleft palate, coloboma

ASD=atrial septal defect, ASV=aortic stenosis, va