

A case report on holt-oram syndrome (heart-hand)

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Abstract

BACKGROUND: The Holt-Oram Syndrome (HOS) or the Heart-Hand syndrome is considered as an overt autosomal hereditary disease with a complete influential effect and variable expression that emerges due to a genetic mutation. It can be vividly characterized by heart disorders and deficiencies in hand structure. Despite the existing genetic heterogeneity, the variable integration between HOS and the T-BX5 gene from the T-BOX Gene Complex has been observed during which various mutations have been reported in the affected patients. The T-BOX Gene Complex is located on chromosome 12 (12 q 24.1), and is able to encode a copying factor. That has a conservative motive with 180 amino acids. The deficiencies in only 1/3 of patients have been observed caused by the mutation of this gene.

CASE REPORT: This case was a 10-year-old child with hand disorders, incomplete growth of clavicle, moving problems in elbow joint and shoulder, disorder in ventricle and auricle walls. The disease was diagnosed as HOS, based on clinical examination and drawing the family tree diagram. It was impossible to investigate molecular mutation due to inaccessibility to the patient.

CONCLUSION: By investigating the family members and their deficiencies and imaging disorder variables according to different reports as well as parents' state of health, the HOS can be defined as an overt heredity resulting from a new mutation in the germinating layer of sexual cells in one of the parents. There is a weak possibility that the disease results from a mosaic mutation in the male parent's testicle or the female parent's ovum. In this case, the probability for the disease to be repeated in parents' next children will be guessed between 1 and 50%.

Keywords: Holt-Oram Syndrome, Hand- Heart Syndrome, T-BOX.

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Introduction

Atrioidigital dysplasia syndrome is a heterogenic autosomal disease with high rate of interference and different variants (omim#142900).¹⁻⁵ In addition to mutation in genes TBX5 on the long arm of chromosome No. 12 (12q24.1) including less than 1.3% of syndrome cases of HOS, there are also different investigations to find other genetic factors that may cause flow type of HOS. One of these genes is TBX3 which may be included with TBX5 in T-BOX genes. The other reported genes are SLL4 on chromosome 20 which rather than creation of the heart and hand disorders may cause dimorphism in ears and lead to hearing disorders.^{6,7} Furthermore, some lotuses have been introduced on chromosome No. 14 (14q23-24.1). Any recognition of all heritage factors and genetic changes including losses up to some replacements which may cause atrioidigital dysplasia will help to prevent any birth of children

suffering from it.⁸⁻¹¹ The following report may help to have a better recognition of this disease.

Case Report

Family history of patient

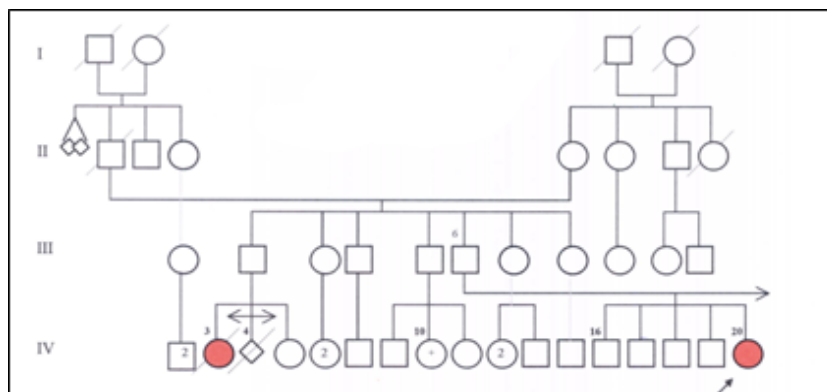
The patient (IV/20) was the 5th child of the family. At her birth time, her father was 33 and her mother 29 years old. The patient had four elder brothers between 15-18 years old. The eldest brother had a local seen dactyl (incomplete) between the 2nd and 3rd fingers of the foot.

Her father (III/6) had a nephew (IV/3) born with a cardiac failure. Her major carotid artery was deformed and died after a cardiac surgery at 14 years old. Then, after 7 years, his brother's wife had an ectopic pregnancy with different abortions. She gave birth to a healthy daughter 10 years later. Even one of his brother's daughters (IV/10) had a mature death with unknown reason. Her family history did not show anything else (Pedigree I).

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Pedigree 1 (parental)

Patient's mother (III/29) had a cousin (III/17) who inherited a renal disease from his mother who was not a relative of patient's mother. There was a complete different cardiac disease (ASDI, mitral cleft) in one of the relatives (IV/22). One of her mother's uncle's daughters (II/22) died from a heart disorder associated with cyanosis very soon. Other members of relatives had no more problems. The relatives' relation was unknown. (Pedigree II)

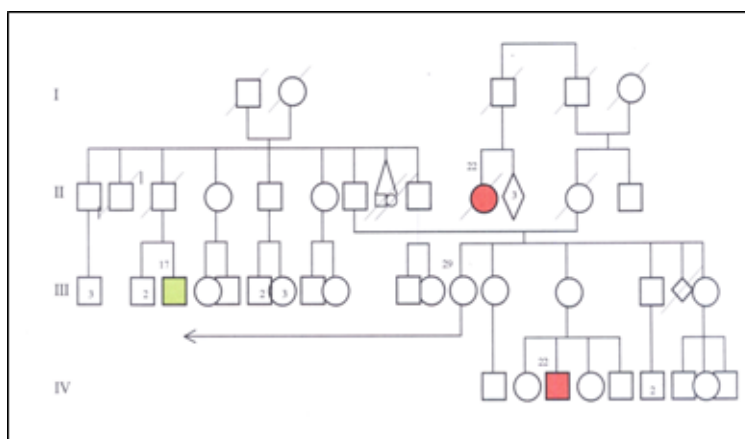
Pregnancy, Birth and Infant Period

There was a pregnancy even with IUD which was exited later on. At the beginning of pregnancy, father has painted the house with a poisonous color (Xyladecor). Mother was infected with a dermal disease at the sixth month of pregnancy.

After calculating the term period and exiting green colored amniotic liquid, the patient had a quick birth. The patient had a length of 53 cm and weighted 3580 gr. There was not any measurement of her head round. After the birth, lack of thumb of the left hand and little

growth of right hand's thumb were noticeable (Figure 1-3). On the 2nd day of birth, unnatural heart voice was heard. On the 17th day of birth, the patient was visited at a medical center. Then, it was specified that there were two shortages at atrium type II and a shortage at ventricle and lung artery.⁴

The patient had a mental and physical growth in compliance with her age. At 6-months, she started to grasp her toys. But, due to the lack of power in her arms, she was treated with physiotherapy. When she was 13-months, she could walk. Even she had growth of teeth and speech with so much interest in cleanliness in compliance with her age and natural growth. She had a surgery on her left hand when was 15 months through which her thumb was replaced with a second finger. The mentioned surgery did not result in satisfaction of her mother and herself because it was difficult to grasp articles while in the past she could do the same task easily (Figure 2). Professor Wilhelm performed the said surgery at Munich-Germany.



Pedigree 2 (maternal)



Figure 1. Little girl while writing showing the compatibility with right hand thumb difficulty.

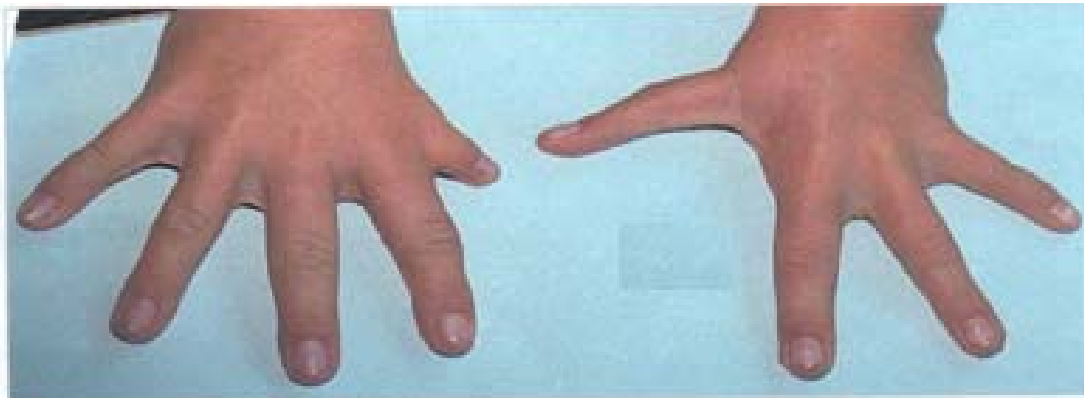


Figure 2. A comparison of left and right hands after surgery .



Figure 3. Incomplete thumb of right hand.

Furthermore, patient had a hyperplasia and dysplasia at her shoulder girdle and elbow joint (Figures 4 and 5). She could not raise her arms at shoulder joint more than 90° and /or turn her leg around her elbow joint (Figure 6). Her shortage of

ventricle was removed by a surgery when she was 9 years old. There were no more problems after that without any need to take any medicines. Regarding all signs and symptoms, she was diagnosed with atriodigital dysplasia. Therefore, in case of her

marriage, we will have Tree No. 3 for her children situation. It means 50% of her children will have healthy genotype and phenotype and 50% of them will be heterozygote and carrier of the gene.

Holt-Oram Syndrome (atriodigital dysplasia syndrome)

This syndrome was defined for the first time in 1960.¹ It includes a set of cardiac disorders and thumb aplasia and/or hypo-plasia which may arise in variety forms (different explanations) and with relative frequency of 1:100,000.^{3,4,12-14}

Skeleton disorders may usually appear symmetrical and/or non-symmetrical in different cases. There are thin and bending shoulders with limited possibilities for turning of elbow joint which is probably related to

hyperplasia of ulna in the length of thumb finger and secondarily, with radius in length of small finger, little growth of clavicle, anomaly of shoulder girdle, additional bones in wrist as other signs of this disease.^{2,5,9,10,11,15,16} Any mutation in TBX5, TBX3, TBX20SL4 may cause pleiotropy related to HOS syndrome.^{8,10,11,17,18}

The relevant signs of HOS in heart are shortage of atrium with arrhythmic and bradycardi, shortage in ventricle walls, and tetralogy of fallot.^{3,4,5,19} In some cases, they have thumb inflation towards its end. In 95% of family cases, any creation of cardiac shortage would be accompanied with some shortages in radius.²⁰⁻²²



Figure 4 and 5. Defects in clavicle and shoulder girdle anomaly.



Figure 6. In this figure any difficulty in movement of shoulder joint and arm is completely obvious especially with bending fingers.

Mostly, like the patient presented here, there are shortage in ventricle type II and/or shortage in atrium wall or mitral bend. Even any mistake in transfer of irritation may appear in a symbolic form (bradicardia, AU blockade, and practical defect of sinus groups).

There are some other results including Tabatznik syndrome, LEWIS and HARRIS-Osborn due to some similarities in different signs which should be recognized from atriodigital dysplasia. In Okihiro syndrome resulted from mutation in SLL4 gene on chromosome 20q13-13.2,^{12,23,24} the signs are similar to HSO but accompanied with an anomaly in eye muscles (lack of abducens nerve and disorders in eye movement). As a result, there will be a problem in site seeing towards left and right sides.¹ Rather than tipped hand and cardiac problems, there are also some shortages in external ear with some hearing disorders and tipped rectum in Okihiro syndrome.¹ There are some radius disorders with thrombocytopenia in Thrombocytopenia-Absent-Radius-Syndrome (TAR syndrome).¹⁷ In case of any complete hands hyperplasia, we should consider teratogenic cases.

According to the recent researches, it was obvious that about 30-35% of HOS cases are related to mutation of T-BX5 gene which is located on the long arm of chromosome 12 (12q24.1). There are 9 genes in this gene which include 2-9 coding proteins. T-BX5 protein is an effective factor in copying with 518 amino acids.^{4,13,6} On amino acid in neighboring an amino acid at the end of the amino acid is related to a deep track of DNA and any mutation in it is the real reason of cardiac disorders in HSO syndrome.^{5,6,14} Any change of amino acid at the carboxyl end may create a relationship with small DNA track and cause different shortages in upper organs.^{5,6,12,25}

Microsatellites analysis in those families with diseased persons suffering from HOS may prove the place of other genes and also heterogenic situation of this disease. Different loci are considered such as 14q23, q24, 2 and 12q21-qtr. Different researches with MAPH (multiplex amplifiable probe hybridization) in those patients with lack of T-BX5 mutation shows a great omission in exons 3-9 of two related proteins of T-BOX.² Human being genome has 7 genes (T-BX7-T-BX1) in T-BOX. The mutation of T-BX3 gene is the real reason of any autosomal shortage in radius.^{5,6,26,27}

Up to now there are some reports about 15 reducing mutations of T-BX5 which are mainly of nonsense type and/or frame shift. For laboratory recognition purpose, it is enough to consider exons No. 7 of T-BX5 gene. But, it is recommended to study SLL4 gene as well.^{7,16}

Discussion

HOS syndrome and/or atriodigital dysplasia syndrome is an inherited autosomal disease with high rate of interference and different variants (omim#142900).¹⁻⁵ The position of gene is on chromosome 12 (12q24.1). Some researches may point out to other gene places as a reason of heterogenic situation of disease. A complete image of disease including cardiac disorders and tipped hands may be appeared in mutational changes at both ends of amine and carboxyl 518 amino acid T-BX5 gene out of T-BOX gene in the above-mentioned locus. This protein is a copying factor. By the way, this is appeared only in one third of patients which are related to the mutation of this gene. All family members have some disorders in their organs without any signs of any cardiac disorders due to the variance and may transfer a complete syndrome to their children. We are not sure whether all people with cardiac demonstrations and without involvement of moving organs are carrier of the same gene or not and whether they could transfer a complete image of disease to their children or not. Due to current information, it is impossible to accept all specified cardiac shortages in this tree; i.e., those in the patient's nephew of grandmother's father (II/22) and her cousin (IV/22) in mother's tree and her uncle's daughter (IV/3) in father's tree in order to have a limited explanations of genetic signs in patient. This is because their pathology has been specified with relevant disorders and the reported signs specific for HSO syndrome are different in references. Even it assumes that the father, mother, sister and brother of the patient are not subject to this gene deformation because they do not present any clinical signs of HSO syndrome as well.

The present gene change in HOS syndrome related to the female patient is probably due to a new mutation with divisions of creating layer of a parent. The probable rate of repeating this case in the next pregnancy is about 1%. This is related to the probable mosaic of creating layer of the parents which are not explained and have been reported in references only for one time.²² For future sisters and brothers of patient according to the drawn trees, we have no more probable situation of repeating. The patient may transfer this mutation to half of her children with the probable pedigree 3. Pre-born recognition is possible by the help of ultra-sonography and echocardiography and also molecular methods. A separated recognition of atrium and other infant disorders with thumb anomaly and resulted difficulties out of thalidomide is so much important.

The only practical method of treatment is through modifying any cardiac and organic shortage.

Conflict of Interests

Authors have no conflict of interests.

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