The Turkish Journal of Pediatrics
Volume 22 / Nos 3-4 / July-October 1900 / pp. 50 - 58

Holt-Oram Syndrome

(Analysis of Six Cases)

Ergül Tunçbilek, M.D.* / Şencan Özme, M.D. / Aytekin Besim, M.D.*** / Sevim Balcı, M.D.***

Association of congenital heart disease and skeletal malformations are found in a variety of syndromes. In 1960 Holt and Oram described a specific hereditary syndrome consisting of congenital heart disease and certain anomalies of the upper extremities.[1] Although the most commonly seen cardiac malformation is atrial septal defect, a wide spectrum of cardiac malformations have been described in this syndrome. Similarly skeletal malformations also show wide variations.

In this paper six cases with Holt Oram syndrome seen at Hacettepe Medical Center are presented and findings are compared with those previously reported (Table I).

Case Reports

Case 1: E.T. 631423. A one month old boy was seen at the Hacettepe Children's Hospital because of finger anomalies. His weight was 4500 g. and height 56 cm. His thumbs and their metacarps were bilaterally absent (Figure 1). On the left 2nd-3rd intercostal space, second degree systolic murmur was heard.

Chest radiography and electrocardiography showed biventricular hypertrophy. Cardiac catheterization revealed an atrial septal defect.

Case 2: H. E. 804257. A day-old boy was referred to the Hacettepe Children's Hospital because of agenesis of the thumbs and deformity of the hands. His height was 58 cm., weight 5 kg. and head circumference 39 cm. On ausculation there was 2 nd degree systolic murmur on the left 3-4 th intercostal space. Electrocardiography showed right axis deviation and right ventricular hypertrophy. An X-Ray of the chest revealed global enlargement of the heart. Radiography of the hands showed that thumbs, their metacarps and radius were bilaterally absent (Figure 2).

* Professor of Pediatrics. Department of Clinical Genetics.
** Professor of Pediatrics, Pediatric Cardiologist
*** Associate Professor of Radiology.

TABLE I

Case No.	Prot.	Sex	Age	Family History	Cardiac Abnormality	Skeletal Abnormalities
1	631423	M	1 month	—	ASD (by catheter)	Thumos and their metacarps absent bilaterally
2	804257	M	41 days	—	VSD	Thumbs, their metacarps, and radius absent bilaterally
3	854348	M	1 year	—	VSD+PH (by catheter)	Finger-like thumb at left. Its metacarps and radius absent. Radial polydactyly at right
4*	323942	F	9 years	+	ASD (by catheter)	One finger with two phalanges on the shoulder
5	437312	M	15 years		VSD	Carpal bones radius and elbow abnormalities
6	674864	F	20 years	+	ASD+Abnormal venous return (by surgery)	Thumb its metacarp and radius absent. Small humerus. Elbow and shoulder abnormalities

* This case was reported by N. Cevik et al[14]

ASD = Atrial septal defect
F = Female
M = Male
PH = Pulmonary hypertension
VSD = Ventricular septal defect

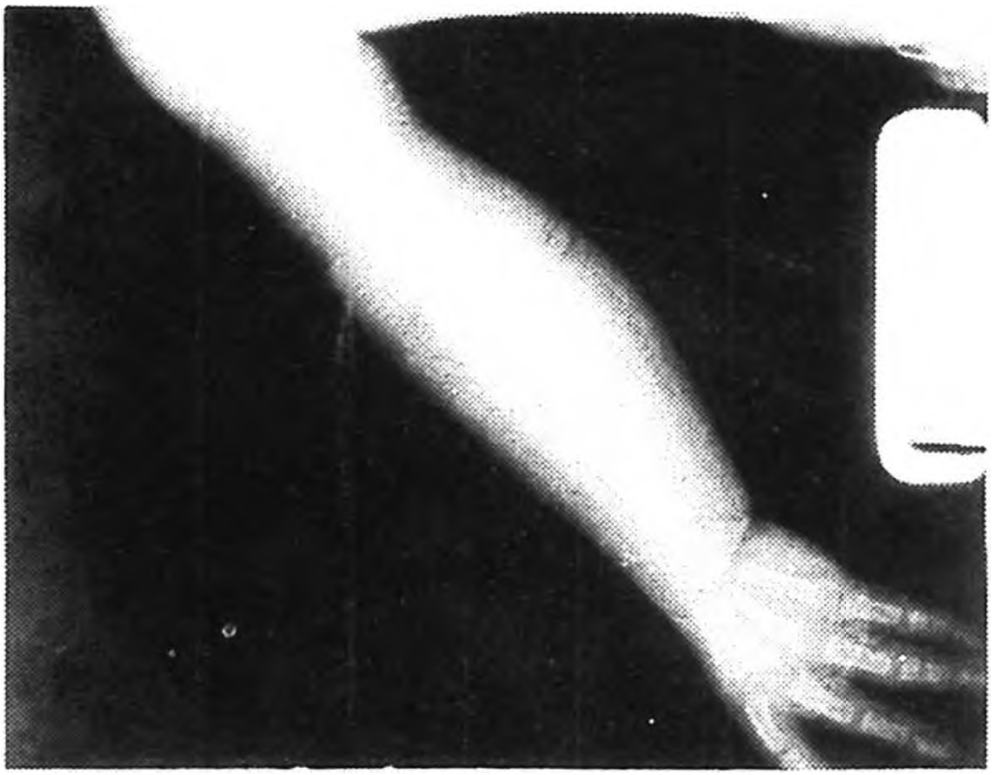

Figure 1
Case 1, thumb and its metacarp are absent

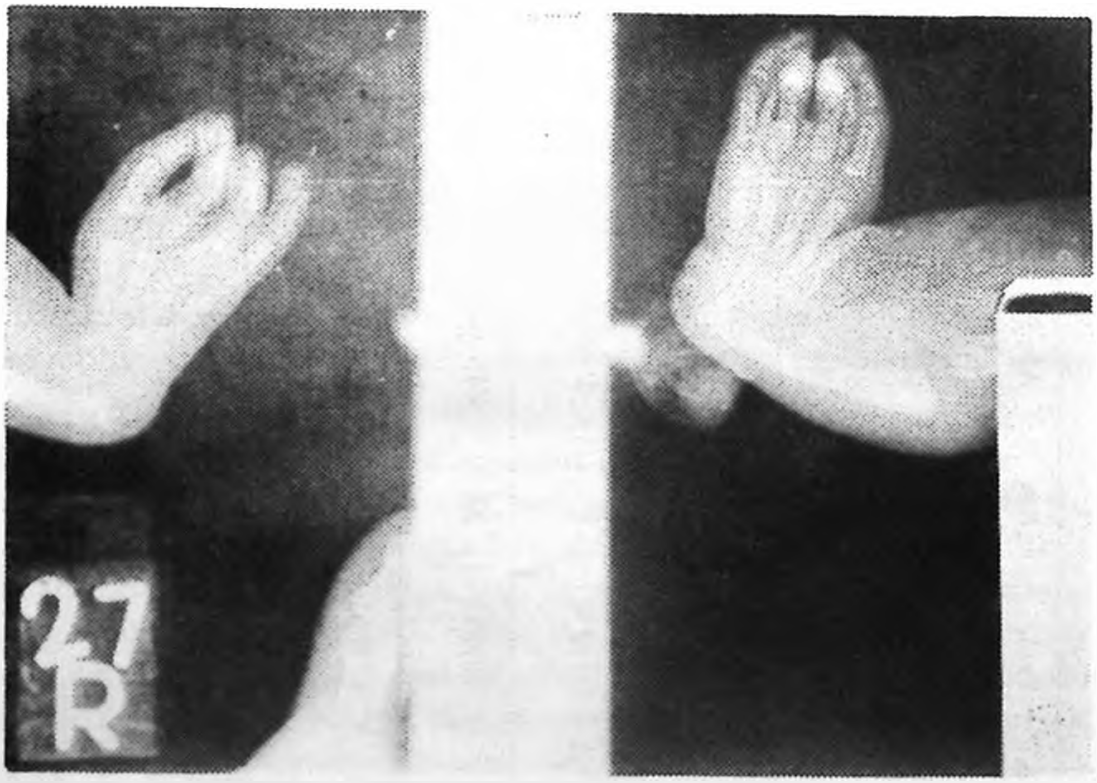

Figure 2
Case 2 thumbs, their metacarps and radius are absent bilaterally

Case 3: H. Ç. 854348. An eight-month-old boy was admitted to the hospital with the complaints of hyperpnea and cyanosis while he was crying. His weight was 4.3 kg. height 62 cm. and head circumference 40 cm. In physical examination third degree systolic ejection murmur was heard on the left 3 rd intercostal space. Well developped radial polydactyly at right hand and finger-like thumb at left were observed. Its metacarp and radius were absent radiologically (Figure 3).

Figure 3

Case 3, fingerlike thumb at left, its metacarps and radius are absent. Radial polydactyly at right

Teleradyogram and EKG showed biventricular hypertrophy.

Ventricular septal defect and pulmonary hypertension was diagnosed on cardiac cathetherization.

Case 4: 323942 A 9-year-old boy, was brought to our clinic with the complaints of deformity of his hands and arms.

He had one finger with two phalanges attached to the shoulder bilaterally.

On the auscultation of the heart the second degree systolic ejection murmur was heard at the upper left sternal edge and the second heart sound was widely split. Electrocardiography showed right ventricular hypertrophy. A plain chest roentgenogram showed cardiomegaly and pulmonary over circulation.

The diagnosis of atrial septal defect was confirmed by the cardiac catheterization.

Case 5: A. A. 437312. A fifteen-years-old boy was admitted to the Hacettepe Children's Hospital with the chief complaints of deformity of arms. His weight was 26 kg., height 135 cm. and head circumference 48 cm.

There were limitation of the extention of the elbow and limitation of the pronation and supination of the forearms bilaterally. He also had carpal bone, radius and elbow abnormalities (Figure 4).

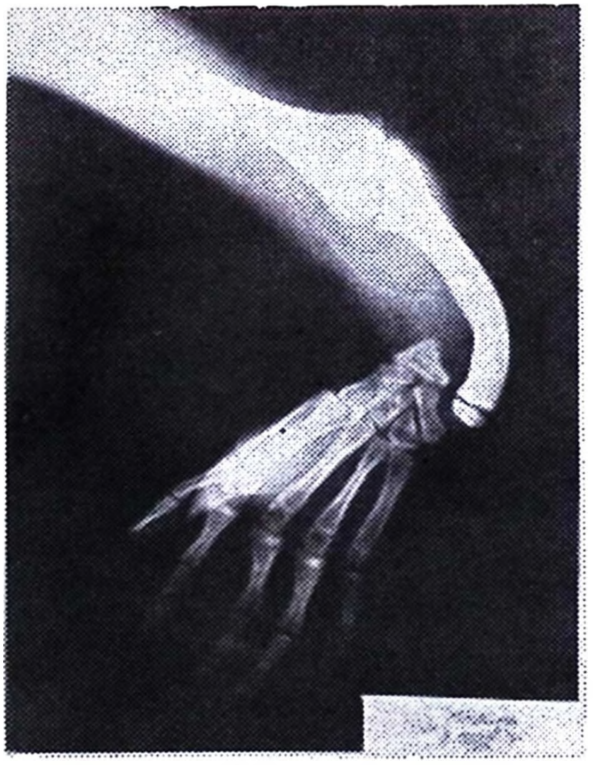

Figure 4
Roentgenogram of the hand of the Case 5

On the auscultation of the heart the pansystolic murmur 3°/VI was heard on the left 4-5th intercostal space. Electrocardiography and X-ray of the heart were normal. The small ventricular septal defect was diagnosed.

Case 6: Z. B. 674864 Twenty-year old girl. She came to the Hacettepe Children's Hospital with the complaints of deformity of her hands and arms. Physical examination revealed a well developed girl. Her thumbs, their metacarps and the radius were absent bilaterally. She also had elbow and shoulder abnormalities and humerus was very small (Figure 5,6).

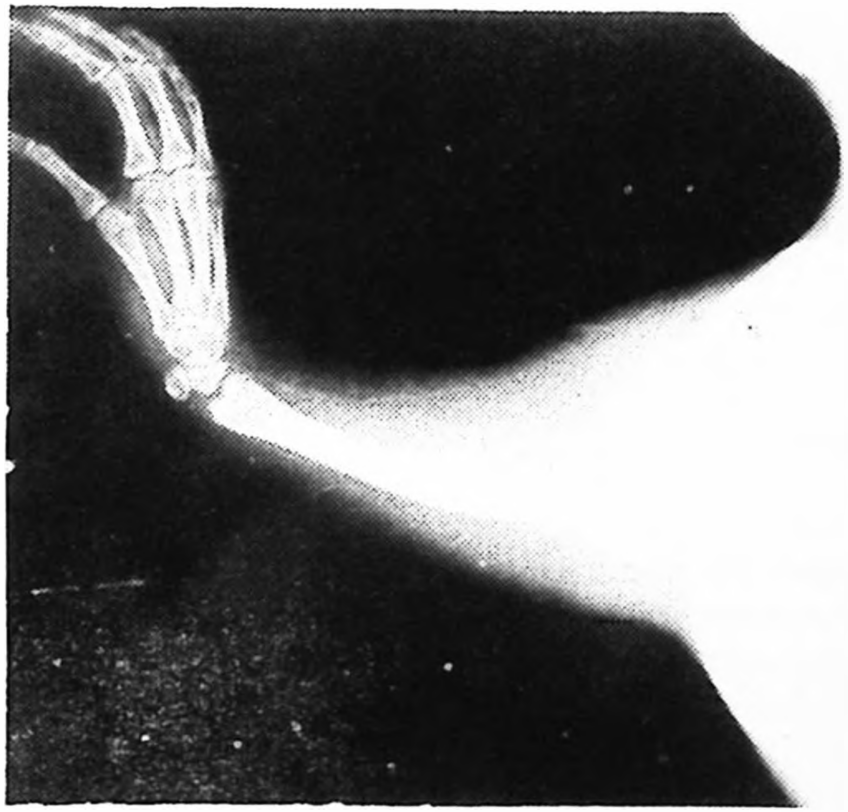

Figure 5

Roentgenogram of Case 6 showing severe shoulder, humerus and elbow abnormalities

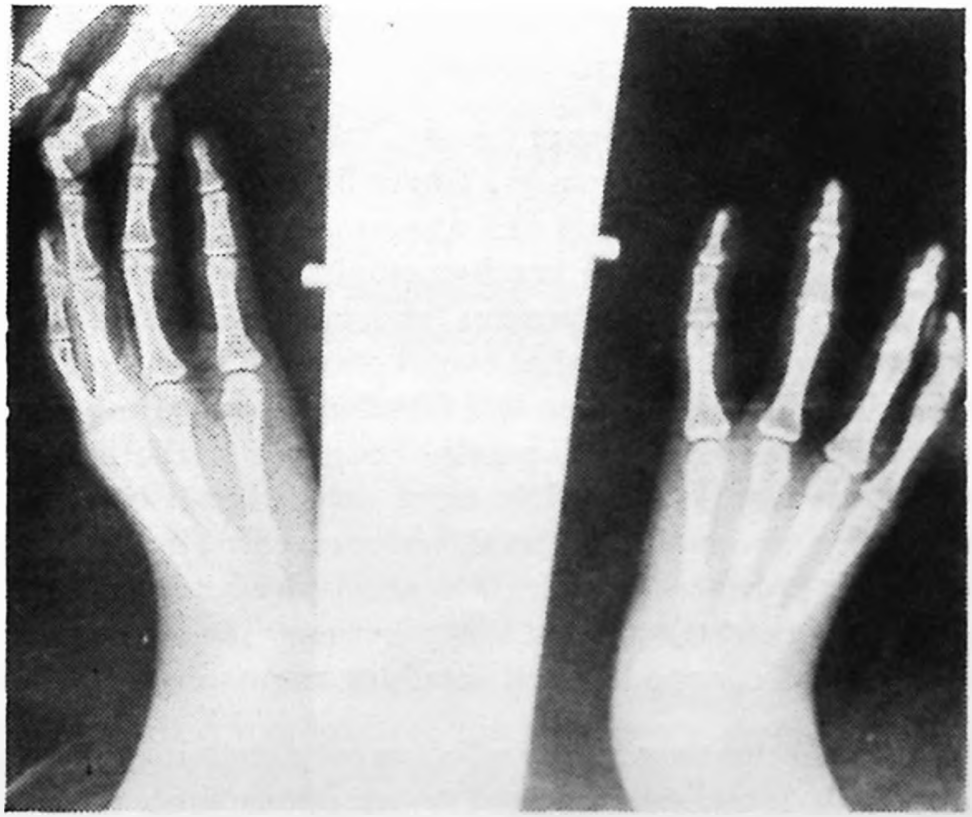

Figure 6

Roentgenogram of hand of case 6 Thumbs and their metacarps are absent

The second degree systolic ejection murmur was best heard on the left 2 nd. 3rd. intercostal space. The second heart sound was widely split and fixed in all phases of respiration.

Electrocardiography showed right ventricular hypertrophy. She had cardiac enlargement and prominent pulmonary artery with increased intrapulmonary vascular markings on standard chest-X-ray. Cardiac catheterization revealed atrial septal defect and abnormal pulmonary venous return. Cardiac malformations were corrected by surgery.

Discussion

The original case described by Holt and Oram, had atrial septal defect, but later other cases with ventricular septal defect, endocardial cushion defect, coarctation of the aorta, and patent ductus arterious were described in this syndrome. In some cases pulmonary hypertension was associated with these anomalies. Coronary vessel anomalies, retroesophageal right subclavian artery, transposition of great vessels and truncus arteriosus were also described in some cases.[2,3]

The congenital heart disease in three of our cases was atrial septal defect and in another three, ventricular septal defect. Anomalous pulmonary venous return was additionally found in one of our cases with atrial septal defect and there was pulmonary hypertension in one of the cases with ventricular septal defect.

The clinical manifestations of the skeletal anomalies are well described in other literature; they include a finger-like triphalangeal thumb or absent thumb, sloping shoulders and abnormalities of the elbow Clinodactyly of the fifth finger and brachymesophalangy are also frequently seen. As a more extreme involvement phocomelia has also been described.[3,4] Poznansky et al. stated that carpal anomalies are more characteristic of the Holt-Oram syndrome and therefore important to the radiologist in suggesting the correct diagnosis.[5] Scaphoid malformation is the most common wrist anomaly while extra carpal bones or carpal fusion may also be seen. Anomalies of the shoulder revealed by the X-ray were also common in Poznansky's series. Coracoclavicular articulation, small scapula, shallowness of the glenoid fossa, accessory bones about the shoulder were the most commonly seen shoulder anomalies in his series.

Skeletal malformations mostly affect upper extremities and therefore the syndrome is sometimes referred to as upper limb cardiovascular anomaly. However in one of Poznansky's case and in the case of Moguilewsky et al. anomalies of the lower extremities were also described.[5,6] In

Moguilewsky's case there was an index finger polydactyly and a hypoplastic thumb on the right hand and one extra toe on each foot. The associated cardiac anomaly was atrial septal defect. As far as we know this is the first case in which polydactyly was described. In one of our cases in addition to radial agenesis at the left, radial polydactyly of the right hand was also present. The associated cardiac anomaly in this case was ventricular septal defect and pulmonary hypertension.

The other skeletal malformations of our cases were similar to those reported in the literature involving mostly carpal bones, thumbs, radii, and shoulders.

In the clinical series the most common malformations associated with cardiac anomalies were skeletal malformations. In a study by Greenwood et al. of 1566 children with congenital heart disease, skeletal malformations were present in 8.8 % and only one case with Holt-Oram syndrome was described in this series.[7] In a series collected in our hospital skeletal malformations were found in 16 % of 104 cases with congenital heart disease and there was no Holt-Oram syndrome cases in the series.[8]

The syndrome is transmitted by an autosomal dominant gene with varying expressivity. Both skeletal and cardiac malformations show varying severity among the members of a family. In our series, one case with positive family history had a sister who died when she was 3 years old. Her hand was connected to her shoulder, but the family did not know whether she had cardiac anomaly or not. The other case had a father with no radial bones and there were two carpal bones on the right hand and three on the left. The humerus and thumbs were hypoplastic. Although nothing was detected in the cardiac catheterization, there was a second degree murmur along the left sternal border and 1° atrio-ventricular block in the electro-cardiogram. In the remaining 4 cases in our series de novo mutation was responsible for the syndrome.

Abnormalities of the heart and musculoskeletal system are associated in a number of syndromes, including Ellis-van-Creveld, Marfan, trisomies of chromosomes 13 and 18 as well as 21. They are also seen in the XO, XXXX and XXXXY chromosomal constitutions[9-11] Fanconi aplastic anemia, thrombocytopenia with absent radius syndrome (TAR) and Thalidomid syndrome must also be considered in the differential diagnosis.

Ockey described a deletion of the long arm a group B chromosome in one case.[12] Similarly Rybac et al. described many cases in four generations in one family and concluded that partial deletion of the long arm of a B group chromosome was related to this syndrome.[13] We analyzed

the chromosomes in one of our cases, the results of the chromosome analysis were normal.

The diagnosis of the Holt-Oram syndrome is important both for the search for cardiac anomalies in the patients with skeletal malformations and for the purpose of giving genetic counselling to the family.

Summary

Six cases radiologically and clinically diagnosed Holt-Oram Syndrome are reported. Two of the cases are familial and the others are caused by de novo mutation. One, has preaksial polydactyly which is an uncommon finding in this syndrome.

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