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A CASE OF HOLT-ORAM SYNDROME SEVERELY AFFECTING THE SKELETON OF THE UPPER LIMBS*

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The Holt-Oram syndrome, a common genetic expression of a large variety of upper limb deformities and congenital defects in the cardiac septa, was first described in 1960[1]. In 1973 Gardner et al[2] reported a case of this syndrome in which the upper appendicular skeleton was severely affected.

In this report we describe a still more severe expression of the mutant gene concerning a father with axial ectromelia and his daughter with amelia, phocomelia and congenital atrial septal defect. This probably represents the most severe case of its kind to be reported to date.

Case Reports

The proband, P.B., (Figure 1), a nine-year-old girl and the third child of the family, was born to an apparently normal mother after an uncomplicated pregnancy; the

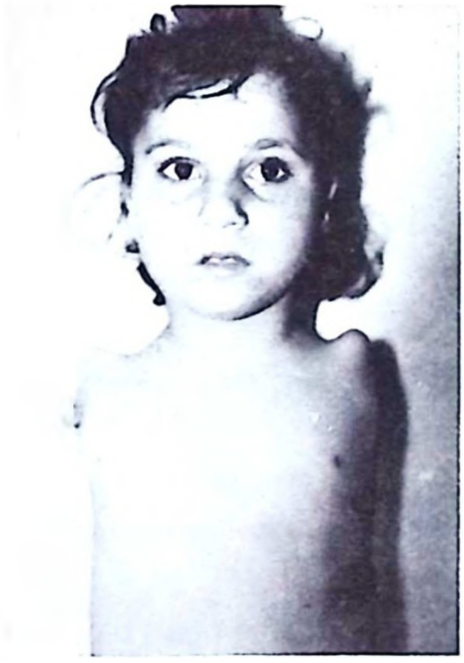

Figure 1

The patient. Note the absence of the upper limbs and the rudimentary finger.

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delivery was normal. Both of the girl's upper extremities were absent except for a rudimentary finger consisting of two phalanges attached directly to the right shoulder by a fibrous band. The lower extremities were normal. A pectus excavatum deformity was also noted. There was a grade III/IV pulmonary systolic ejection murmur. No thrill was detected.

Radiological examination of the chest revealed a moderately enlarged heart with dilated right and left ventricles. Engorgement of the peripheral pulmonary arteries was demonstrated and a segment of the main pulmonary artery was prominent. Both scapulae were hypoplastic and high-set. There was no bone formation distal to the left scapula and only two phalangeal bones were present distal to the right scapula. The clavicles were shortened; their lateral thirds had upward curvature with distal angulation (Figure 2). Radiological examinations showed that the skull, vertebrae, pelvis and lower extremities were entirely normal.

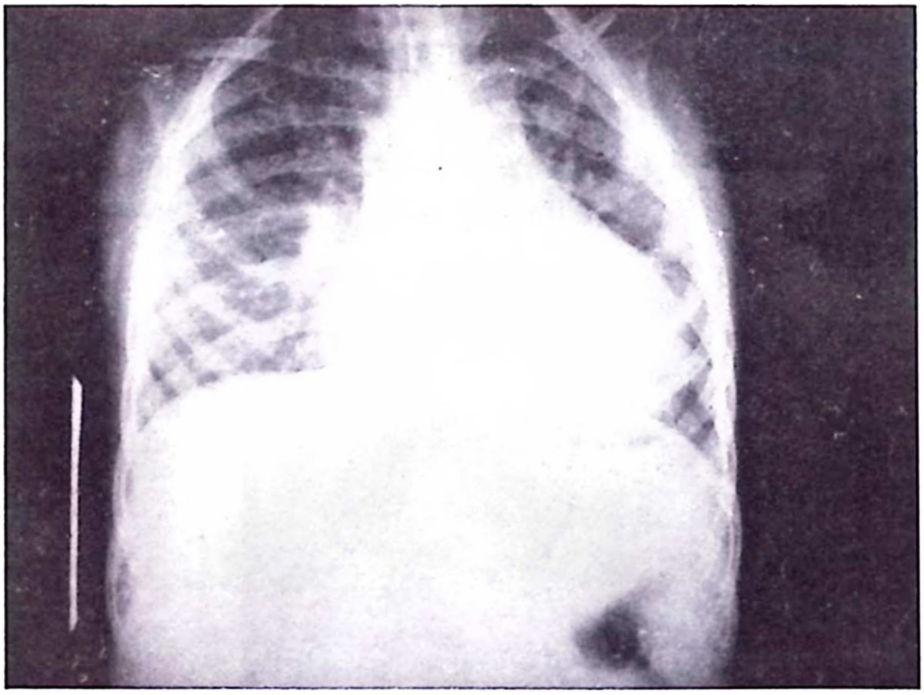

Figure 2

Chest X-ray of the patient showing enlargement of the heart.

Electrocardiography showed a first degree heart block with right axis deviation and mild right ventricular hypertrophy (Figure 3). Right ventricular hypertrophy of the outflow type was diagnosed by vectorcardiography.

Left and right cardiac catheterizations and cineangiography demonstrated a left to right shunt at the atrial level. In the right ventricle and in the pulmonary artery the systolic pressure was elevated to 50% of the systemic pressure; these findings indicated the presence of an atrial septal defect.

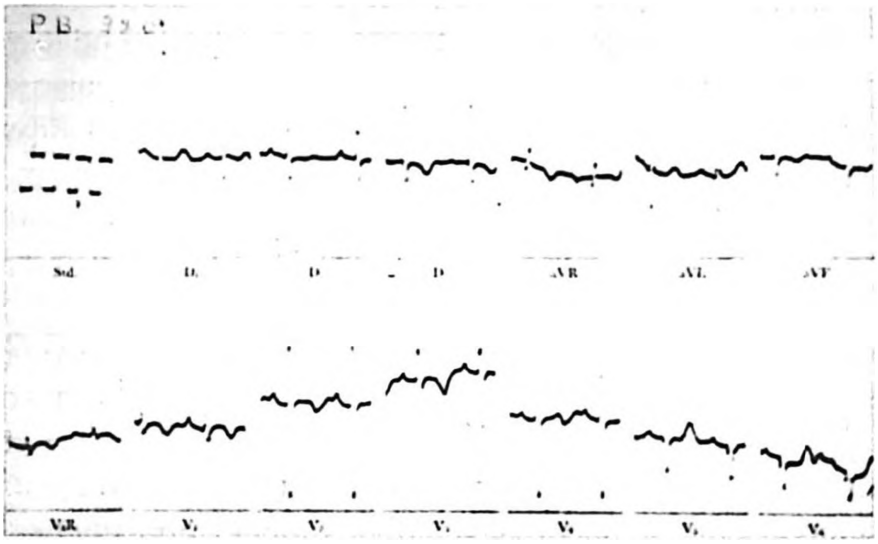

Figure 3

ECG findings of the patient.

The proband's father, M.B., (Figure 4), was a 38-year-old white male. Both his arms were short, the proximal and distal parts in both being undistinguishable and the hands, which were held in anteflexion, were attached to the distal portions. There

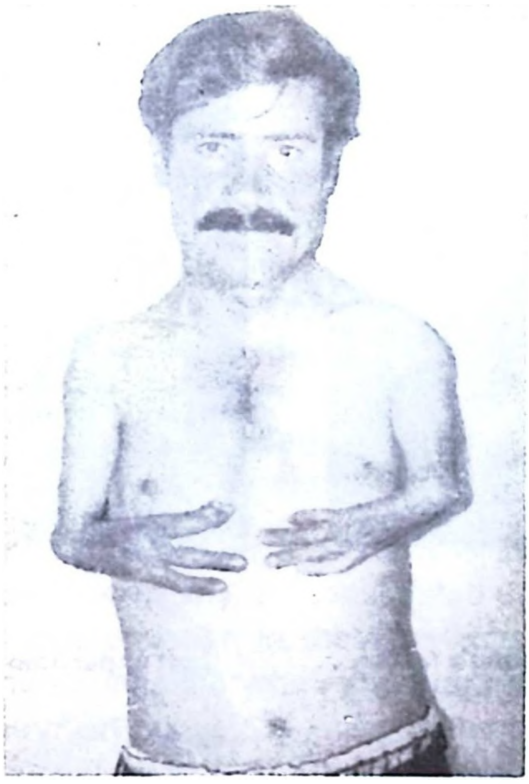

Figure 4

The proband's father showing bilateral phocomelia.

was no thumb. There was synostosis between the second and third fingers of the right hand and the second finger of the left hand was short. The lower extremities showed no abnormalities. There was mild pectus excavatum, also a II/VI degree soft midsystolic murmur radiating slightly both upwards and downwards. The secondary pulmonary sound was split. Radiological examination of the chest revealed clear lung fields and a normal heart. There was scoliosis with a right concavity. Both scapulae were hypoplastic, set higher than is normal and more laterally. The X-rays of the upper extremities revealed markedly hypoplastic humeri. They were approximately 5 cm long, abnormal in configuration, articulating neither with the scapulae nor at the elbows. The radial bones were absent in both instances. There were only two carpal bones in the right wrist and three in the left wrist. Other findings included aplasia of the first metacarpal bone of each hand and of the thumbs. The second right metacarpal bone was longer and thinner than normal, and there was synostosis between the second and third fingers. Radiologically the pelvis and the lower extremities were normal (Figures 5,6).

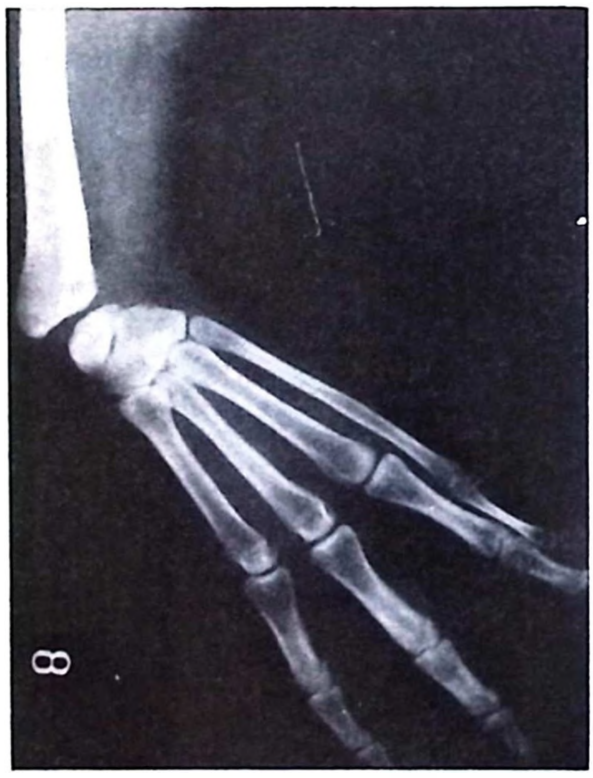

Figure 5

Right upper limb of the proband's father.

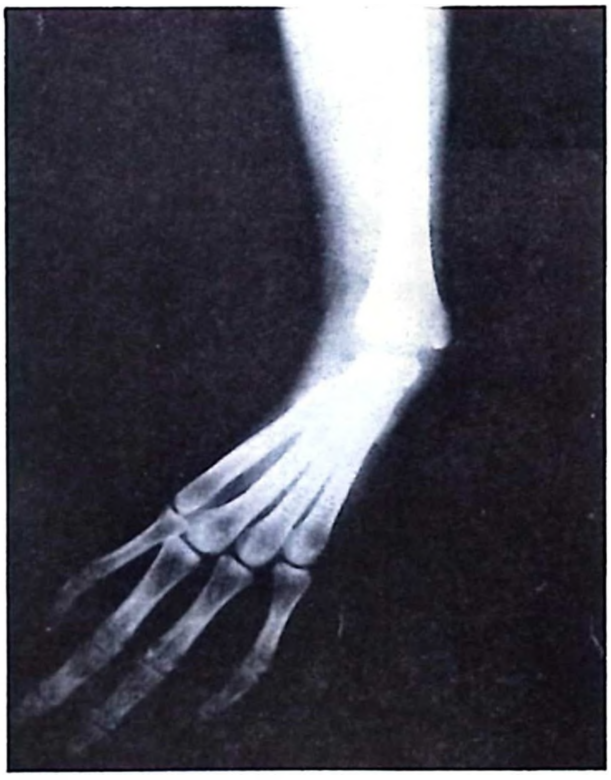

Figure 6

Left upper limb of the proband's father.

The ECG demonstrated a first degree atrioventricular block, dilation of the right atrium and a partial right bundle branch block. Cardiac catheterization demonstrated no left to right shunt nor any other anatomical defect.

Chromosome analysis of the proband and her father revealed no abnormalities.

An eleven-year-old girl and a six-year-old boy, siblings of the proband, were found normal in physical and laboratory examinations. There had also been another apparently normal boy who had died, aged five months, from an unknown cause and the mother had also aborted a fetus, but it was not known whether this was affected or not.

A physical examination of the proband's mother performed six years earlier had been within normal limits, but on re-examination the heart was found to be moderately enlarged and there was a pre-systolic, late diastolic murmur over the apex which radiated outwards and the second sound was split. ECG revealed atrial fibrillation, ectopic ventricular beats, right ventricular hypertrophy and digital effect. Teleradiograms of the heart showed enlargement in transverse section, and especially dilatation of the left atrium and the left ventricle. The main pulmonary artery and hilar pulmonary arteries were prominent. There was stasis in both lung fields. Mitral stenosis due to rheumatic fever was diagnosed clinically. The skeletal survey did not reveal any abnormalities.

Dermatographic findings: the digital type, palmar and plantar mainlines and the scores of various dermatoglyphic analyses of the family are set out in Table I. All members of the family had whorls on most fingertips. The total ridge count was high. Intermedially or distally displaced axial triradii were present. The proband had a whorl on the volar surface.

Discussion

Since its initial description in 1960, many instances of the Holt-Oram syndrome from different parts of the world have been described[2-6], and it is apparent that the the malformations involving the extremities as well as the heart vary in severity from patient to patient even within the same family. Our case appears to be more severe than those so far published. In 1973 Gardner et al[2] reported another such similar case of a rudimentary upper limb segment consisting of one metacarpal and two phalanges attached to the left shoulder and a short arm with three fingers, three metacarpal bones and phalangeal elements on the right.

It is well established that the Holt-Oram syndrome is inherited as an autosomal dominant trait with variable expressivity. It is postulated that the mutant gene interferes with normal organ differentiation in these patients somewhere around the fourth to fifth week of intrauterine life when important developments concerning the arms and the primitive heart take place[7]. Since the development of the lower appendicular skeleton occurs at a later date, its normal evolution is not hampered.

It has also been demonstrated by Rybak et al[8] that the abnormalities of the limbs become more severe through the generations and may turn into ectromelia in the

TABLE I

The Scores Connected with Dermatoglyphic Analysis of the Proband and Her Family Members

		Finger Tips												Palms	
		Ridge-Count										Total ridge-count	No. of whorls	a-b ridge-count (sum of both hands)	atd angle (sum of both hands)
		Left					Right								
	No. of fingers	$_{r}V_{u}$	$_{r}IV_{u}$	$_{r}III_{u}$	$_{r}II_{u}$	$_{r}I_{u}$	$_{r}V_{u}$	$_{r}IV_{u}$	$_{r}III_{u}$	$_{r}II_{u}$	$_{r}I_{u}$				
Father	8	24 –	20 13	20 18	25 14	– –	25 12	15 21	28 15	9 16	– –	179	7	–	–
Mother	10	17 17	19 20	23 22	12 26	25 21	17 14	18 21	21 –	17 –	30 14	217	8	96	105°
Sister	10	24 13	27 21	24 18	20 14	29 19	21 15	26 19	24 20	23 13	24 20	242	10	97	87°
Proband	1	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	–	1	–	–
Brother	10	18 –	22 14	18 –	18 9	23 –	16 8	17 18	16 13	20 15	23 –	192	6	122	165°

r = radial site of pattern u = ulnar site of pattern

fourth generation. It is interesting to note in this respect that in our case the father of the proband had relatively mild malformation of the upper extremities and there was no cardiac defect, while in the proband, the upper limb deformities were unusually severe and were associated with an atrial septal defect.

No chromosome studies have been carried out in many of the published cases. Zetterqvist[9], and Lewis et al[7] were able to detect translocations, duplications and minor chromosome abnormalities in their studies. Ockey et al[10] described a deletion of the long arm of a chromosome in the B group in their case where there was severe upper and lower limb lesions and a heart defect. Minor chromosome aberrations were also detected by Rybak et al[8] in a girl and a boy with severe limb abnormalities. In our cases, even though far more severe upper limb defects are present, there were no chromosome aberrations.

An increase in whorls and in total ridge-count on the fingertips has been reported in other cases of the Holt-Oram syndrome[5,11-13]. Distally displaced axial triradii and the simian line have often been seen. According to Rybak et al[8], the findings involving the total ridge-count and fingertip patterns are common features of the Holt-Oram syndrome, whereas those related to the axial triradius and the simian line are characteristic features of congenital heart defects. However, in our patients similar dermatoglyphic findings were observed in the proband and her father as well as in other immediate family members (i.e. mother and siblings). This may indicate that the aforementioned dermatoglyphic findings are no other than a familial trait.

Summary

A family with the Holt-Oram syndrome is described; both the proband and her father had unusually severe upper extremity malformations. The clinical, cardiologic and dermatoglyphic findings of the proband and the family members are discussed and the relevant literature is cited for comparison and contrast. This case is apparently more severe than others of the kind so far to have been reported.

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