Holt-Oram syndrome in a Maltese family

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Summary

A Maltese family is described with the Holt-Oram syndrome.

The association of hand anomalies with congenital heart disease in a patient should be an indication to screen the other members of the family for similar defects.

Introduction

Holt & Oram (1960) linked various skeletal abnormalities with congenital heart disease in four generations of a family. In particular, malformations of the hands were associated with atrial septal defect (secundum type) and bizarre arrhythmias. In 1961, McKusick described a similar syndrome in a mother and daughter and suggested the term 'atrio-digital

dysplasia'. Harris & Osborne (1966) related congenital anomalies of the radius with ventricular septal defect (ventriculo-radial dysplasia).

We describe three members of a Maltese family (Fig. 1) with minor hand anomalies and atrial septal defect. A fourth member of the same family has finger-like thumbs and findings consistent with CHD.

Case reports

Case 1. Male 33 years (III, 4)

A heart murmur was discovered at 9 years of age at a routine school medical examination. He later complained of slight breathlessness on exertion, frequent coughs and colds, and occasional palpitations.

On examination, he was of small build—height

FIG. 1.

160 cm (5 ft 3 in.), weight 57 kg (121 lb). He had no cyanosis, dyspnoea, pallor or oedema. JVP normal. His hands were small, with short fingers, and incurved little fingers; there was no clubbing. The thumbs extended almost to the proximal interphalangeal joint and there were single metacarpophalangeal skin creases. There was a marked right ventricular lift. On auscultation, there were frequent ectopics and a grade 2–3/6 ejection murmur in the pulmonary area with a widely split, fixed second sound. There was no tricuspid flow murmur. The lung bases were clear and the liver was not palpable. The chest X-ray showed moderate cardiomegaly (CTR 63%) with prominent pulmonary artery and marked pulmonary plethora. The ECG showed a varying pacemaker with variable A–V block, incomplete right bundle branch block, right axis deviation and right ventricular hypertrophy (Fig. 2).

At cardiac catheterization, the RV pressure was 30/3 mmHg. The left atrium was entered from the right atrium, and the left ventricle from the left atrium. There was a large left-to-right shunt at atrial level (pulmonary systemic flow ratio 4:1), with equalization of mean pressures in the atria. Cineangiography with injection of contrast medium into the left ventricle excluded ostium primum defect.

Operation. In January 1969 (Mr L. Bromley), under cardiopulmonary by-pass, a large ASD of the secundum type (3.5×2.5 cm) was repaired by direct suture. Some days after closure, atrial flutter occurred which was reverted to sinus rhythm with digitalis. The atrial flutter recurred 10 days later and was reverted to sinus rhythm by DC cardioversion (100 watt-seconds); this was preceded by asystole of

15 sec duration, and followed by various atrial dysrhythmias including slow atrial and slow nodal beats, and atrial ectopics. He still suffers from occasional palpitations.

Case 2. Female 28 years (III, 2)

She was known to have had a cardiac murmur since childhood but has remained symptom-free. In April 1969 she was delivered by ventouse extraction of a male baby (IV, 1) after an uneventful first pregnancy. In October 1969 she had a urinary tract infection and IVP showed a bifid right kidney, larger than the left, and lying low down in position, with slight dilatation of the upper half of the right ureter.

On examination, she was of small stature—height 147 cm (4 ft 10 in.), weight 35 kg (74 lbs). There was no cyanosis, tachypnoea, pallor or oedema and the JVP was normal. She had small hands with slight finger clubbing as well as incurved little fingers. Supination of both forearms was limited to about 120° . Pulse regular and of good volume, rate 60/min. BP 110/70 mmHg. She had slight left chest bulge and marked right ventricular lift and the apical impulse was not displaced. There was a grade 2/6 ejection murmur in the pulmonary area with wide fixed-split second sound and a tricuspid flow murmur was heard best on inspiration. The lungs were clear on auscultation and the liver was not enlarged. Chest X-ray showed gross cardiomegaly with considerable dilatation of the pulmonary artery and pulmonary plethora. The ECG showed sinus rhythm with right axis deviation, incomplete right bundle branch block, and a PR interval of 0.2 sec.

FIG. 2. Case 1. ECG shows a varying pacemaker with variable A–V block, incomplete right bundle branch block, right axis deviation and right ventricular hypertrophy.

X-ray of hands and forearm showed gracile bones with fusion between the scaphoid and trapezium in each wrist.

Cardiac catheterization: PA pressure was raised (38/16 mmHg) and the RA pressure was slightly elevated. A large left-to-right shunt (pulmonary/systemic flow ratio 2.5:1) was demonstrated only at atrial level.

Operation. In January 1970 (Mr L. Bromley) a large secundum type ASD (3.5×2.5 cm) was closed with a patch of pericardium. Her postoperative course was complicated by a bout of atrial flutter which was converted to sinus rhythm by DC shock after anticoagulation.

Case 3. Male 31 years (III, 5)

He had recurrent chest infections during childhood, and occasionally complained of palpitations. A heart murmur was discovered at the age of 15 years. He was otherwise symptom-free except for migraine.

On examination, he looked healthy. Height 160 cm (5 ft 3 in.), weight 54.5 kg (120 lb). There was no tachypnoea, cyanosis or clubbing. His hands showed no abnormality, except that the thumbs extended to the level of the proximal interphalangeal joint. Pulse regular and of good volume, rate 60/min. Normal femoral pulses. BP 130/80 mmHg. His JVP was not raised. A right ventricular lift was palpable, and there was a systolic thrill over the upper left sternal border. There was a grade 3/6 ejection murmur best heard in the pulmonary area, with a fixed-split second sound of normal intensity. There was also a tricuspid flow murmur on inspiration. The lungs were clear on auscultation and the liver was not palpable.

Chest X-ray showed a prominent pulmonary artery with marked pulmonary plethora and cardiomegaly. The ECG showed right axis deviation, sinus rhythm with varying pacemaker and at times nodal rhythm. (Fig. 3).

Cardiac catheterization showed normal right-sided pressures. The left atrium was entered from the right atrium and there was a left-to-right shunt at atrial level (pulmonary/systemic flow ratio 4.5:1). Selective angiocardiology with injection of contrast medium into the left ventricle was normal.

Operation. In September 1969 (Mr L. Bromley) a large secundum type defect (3.5×2.0 cm) was closed with a Teflon patch. Three days after operation he had atrial fibrillation reverting spontaneously to sinus rhythm after 48 hr.

He has remained well on follow-up.

Case 4. Male 2 years 2 months (IV, 1)

Full-term delivery by ventouse extraction at St Luke's Hospital, following a normal pregnancy. There was no difficulty in onset of respiration. A skin 'papilloma' in the midline on the anterior chest wall and bilateral thumb malformations were noted soon after delivery. On both sides, there was an incurved finger-like thumb, inserted more distally than one would expect, lying in the same plane as the fingers (Fig. 4). The major palmar skin creases were abnormal and there was lack of prominence of the thenar eminence. There were initially no signs indicative of congenital heart disease, and repeated examinations until recently failed to reveal any abnormality of the cardiovascular system. When seen at 26 months of age, he looked well and was developmentally normal. Height 86 cm (34 in.), weight 12.6

FIG. 3. Case 3. ECG shows right axis deviation, sinus rhythm with varying pacemaker and at times nodal rhythm.

FIG. 4. Case 4. Incurved finger-like thumbs lying in the same plane as the fingers and inserted more distally than normal.

kg (28 lb) both around the fiftieth percentile. There was a grade 2/6 ejection murmur at the upper left sternal border with a variable split second sound in the pulmonary area. Chest X-ray (Fig. 5) showed cardiomegaly with normal pulmonary vasculature. The ECG showed right axis deviation, right atrial P waves, incomplete right bundle branch block, child R/S pattern in chest leads with voltage within normal limits. X-ray of the hands show (Fig. 6) triphalangeal thumbs; two carpal ossification centres present.

FIG. 5. Case 4. Chest X-ray at 2 years shows cardiomegaly with normal pulmonary vasculature.

FIG. 6. Case 4. X-ray of hands showing triphalangeal thumbs.

Discussion

The association of cardiac with skeletal malformations, especially those of the fingers, has been well documented (Holmes, 1965). The cardiac anomaly is not always associated with a specific skeletal defect. In the Holt-Oram syndrome however, malformations of the hands, mainly of the thumbs and radial side of the wrists are associated with cardiac malformations, most commonly atrial septal defect of the secundum variety, and various arrhythmias. Moreover, the condition is familial and inherited as an autosomal dominant with variable expressivity, in contrast to the usual recessive pattern of familial congenital heart disease (Campbell, 1959).

According to Harris & Osborne (1966) the Holt-Oram syndrome forms one end of a wide spectrum of conditions with cardioskeletal malformations. At the other end of the scale there are cases of ventriculo-radial dysplasia, i.e. VSD associated with absent radii and thumbs. An intermediate group of anomalies with mixed features of both the Holt-Oram syndrome and ventriculo-radial dysplasia, sometimes with severe pulmonary hypertension, also occurs (Table 1).

Although combined cardiac and skeletal anomalies are commonly associated in several of the severe chromosomal disorders (for example, 13-15 (D) trisomy, 17-18 (E) trisomy, Down's syndrome, etc.), no chromosomal abnormalities have been identified in the Holt-Oram syndrome.

Dermatoglyphic analysis in the Holt-Oram syndrome has been reported in a few cases. The thenar eminence is poorly developed with consequent gross disruption of the normal dermal pattern, the axial triradius being displaced distally (Fig. 7).

The cases reported here are the first description of Holt-Oram syndrome occurring in a Maltese

TABLE 1. The upper limb-cardiac syndrome

	Atrio-digital dysplasia (Holt & Oram, 1960)	Intermediate syndrome (Holmes, 1965)	Ventriculo-radial dysplasia (Harris & Osborne, 1966)
Genetic transmission	Familial, autosomal dominant	Familial, autosomal dominant	Not familial
Cardiac anomaly	Usually ASD2° Bizarre arrhythmias	VSD ± endoc. cushion defect ± pulm. hypertension No arrhythmias	Usually VSD ± pulm. hypertension No arrhythmias
Skeletal anomaly			
Radii	Usually normal	Often malformed	Hypo/aplastic
Thumbs	Hypo/aplastic Three phalanges Finger-like Distally placed	Hypo/aplastic Two or three phalanges Often finger-like	Hypo/aplastic Not triphalangeal Not finger-like
Pectus excavatum	Often	Often	Rare

FIG. 7. Case 4. Palmar print showing gross disruption of dermal ridges and distal displacement of axial triradius.

family. Cases 1, 2 and 3 were found to be suffering from atrial septal defect (secundum type) and the minor hand anomalies were not noted originally. However, when Case 4 was born he was noted to have the typical finger-like thumbs of the syndrome. This immediately led us to review the mother and her brothers and the minor hand anomalies found were in fact consistent with this syndrome. All the three affected adults remarked that their father (II, 3) had small 'unusual' hands; he died aged over 70 of a cerebrovascular accident. Their mother (II, 4) had neither hand anomalies nor congenital heart disease. Case III, 1 has minor hand anomalies (see below) but no evidence of congenital heart disease.

Five other members of the family have emigrated and were not available for study.

It is well recognized that patients with ASD often have a skeletal anomaly. In particular, the presence of a hand malformation in a patient with ASD, or in any other member of the family, should be an indication for careful examination of the cardiovascular system in the rest of the family.

The hands may not be obviously abnormal, as in our cases 1-3, but an X-ray of the hands should be a useful screening investigation in all cases of ASD. In Case 2, this revealed fusion between the scaphoid and trapezium in each hand. Minor hand anomalies, even in a known family with the Holt-Oram

syndrome, however, are not necessarily indicative of congenital heart disease. Indeed, R.A. (III, 1) has the left hand which is slightly smaller than the right, and the left middle finger is short and fixed at the distal interphalangeal joint, with absent distal interphalangeal palmar skin crease; yet she has no clinical evidence of congenital heart defect.

Upper limb deformities, especially of the fingers have often been associated with congenital heart disease (Holmes, 1965). In Case 4 initially no cardiac lesion could be defined. On follow-up, however, first cardiomegaly and later a pulmonary ejection murmur have been detected. Indeed, in such cases, prolonged follow up, for several years if necessary, may be required before heart disease can be excluded with certainty.

Acknowledgment

We would like to thank Dr E. A. Cachia, Consultant Paediatrician, for permission to publish details of Case 4.

We are also grateful to Dr E. M. M. Besterman and Mr L. Bromley, of the Cardio Thoracic Unit at St Mary's Hospital, London for the cardiac investigations and surgical treatment of Cases 1, 2 and 3.

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