UPPER LIMB-CARDIOVASCULAR SYNDROME*

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In recent years, the importance of genetic factors has been recognized in the aetiology of some congenital cardiac abnormalities, especially atrial septal defect.[1,2] Roughly one-fifth of patients with congenital cardiac anomalies have extracardiac malformations,[3] but it was the recognition of the familial occurrence of upper limb abnormalities and atrial septal defect by Holt and Oram[4] that provoked increased interest in the implications of such findings. There have been several further reports of this association, with many pedigrees demonstrating autosomal-dominant inheritance.[5-10] It has also been recognized that the cardiac lesions may vary, and may include ventricular septal defect.[5,7] Yet comprehensive reviews[11] fail to discuss this syndrome, and it is partly in order to increase awareness of its occurrence that we now report two isolated cases of ventricular septal defect associated with malformation of the upper limbs.

CASE REPORTS

Case 1

A White girl of Afrikaans stock had been found to have malformations of the upper limbs at birth, and a cardiac murmur and hypochromic anaemia during infancy. The anaemia was corrected with oral iron. She was referred to one of us (B.Z.) at the age of 5½ years for further investigation. There was no history of dyspnoea, cyanosis or impaired effort tolerance. Her mother had not taken thalidomide during the pregnancy, and the parents, grandparents, uncles, aunts and siblings were not affected in any similar way.

The patient was 41 in. (104·4 cm.) tall and weighed 29½ lb. (13·4 kg.). The blood pressure was 110/60 mm.Hg, the femoral and radial arteries were normally palpable, and there were no signs of cardiac failure. The respiratory, nervous and alimentary systems were normal, urinalysis was negative and the haemoglobin was 14 G/100 ml. There were no stigmata of Marfan's, Down's or Turner's syndromes.

Cardiovascular abnormalities. The heart was enlarged clinically, with a tapping apical impulse in the fifth left interspace just beyond the midclavicular line. There was a loud left lower parasternal pansystolic murmur (grade 5/6) and thrill, a pulmonary ejection click, wide but normal splitting of the second heart sound, and a third heart sound, followed by a soft, low-pitched, apical diastolic murmur.

The upper limbs (Fig. 1). The shoulders were normally mobile, but laterally flattened, with prominent acromion processes. The right upper arm was 5 cm. longer than the left, but the left forearm was 1·25 cm. longer than the right. The left elbow could not be flexed more than 135°. Both wrists were acutely inverted, with limited movement possible only laterally, and the thumbs were absent. The fingers were not clubbed. The proximal phalanges of the medial two fingers of the left hand were enclosed in a sheath of skin, and the corresponding fingers on the right were slightly webbed proximally. Movement of the metacarpophalangeal joints of both hands was limited, the lateral two on the right being fixed.

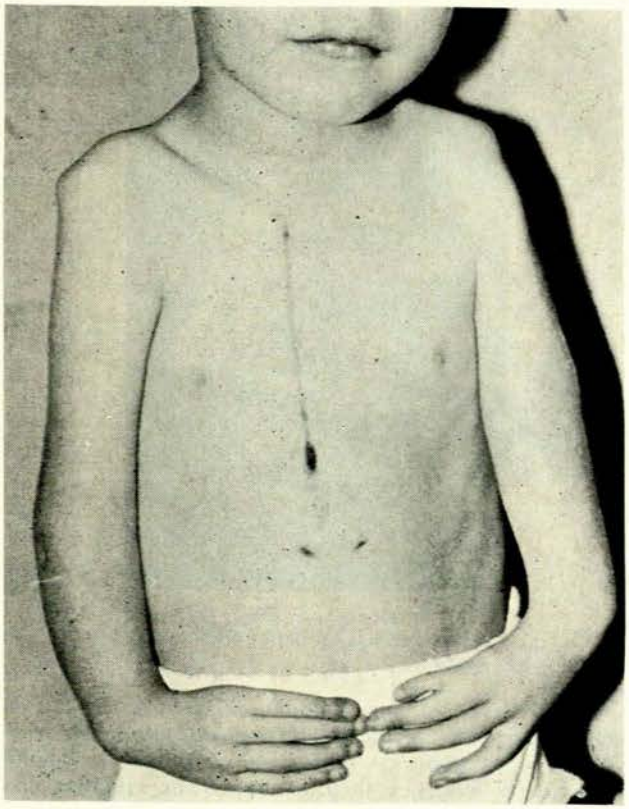

Fig. 1. Upper limb abnormalities, and chest scar due to cardiac surgery (case 1).

The palm and fingerprint patterns (recorded and analysed by Dr J. W. Thompson) were normal, showing no abnormal displacement of the axial triradius of either hand. The radiological changes are shown in Figs. 2 and 3. Features common to both upper limbs were: malformation of the glenoid fossae; complete fusion of the bones of the forearm, the upper end being like that of the ulna, and the lower like that of the radius; only two carpal bones (resembling capitate and hamate); and absence of the metacarpal and phalangeal bones of the thumb. The other metacarpals and phalanges were normal.

Other bone changes were more marked on the left: deformity and lateral displacement of the upper humeral epiphysis; a lower medial humeral exostosis; and a small translucency with sclerosed margins in the proximal part of the forearm bone, 2 cm. from the joint space. The right

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humerus was shortened by 5 cm.; its upper epiphysis was seen as two small faint areas of calcification.

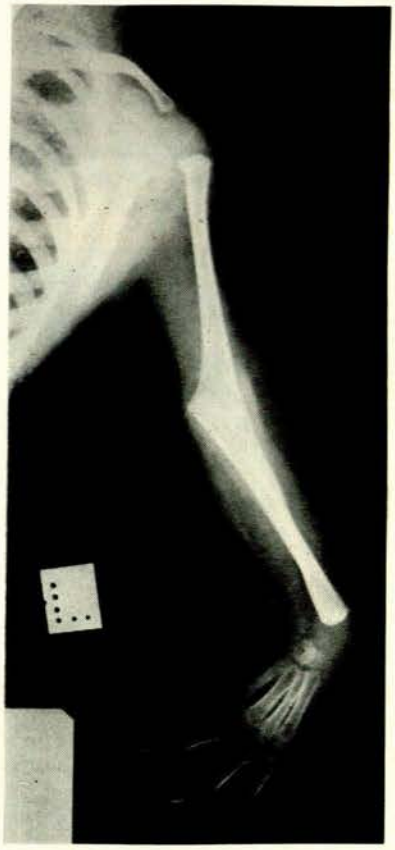

Fig. 2. X-ray showing skeletal abnormalities of left upper limb (case 1).

Cardiac investigations. Radiological studies showed enlargement of both ventricles, a prominent pulmonary artery with vigorous pulsation of its branches, and pulmonary plethora. The electrocardiogram showed sinus rhythm, first-degree AV block (PR = 0·24 sec.), slight right axis deviation, and biphasic T waves in V5 and V6. Cardiac catheterization (Drs W. Beck and M. S. Gotsman, Cape Town) showed a ventricular septal defect with a left-to-right shunt of 50%.

Chromosome studies revealed a normal karyotype (Dr M. M. Friedman).

On 8 February 1966 an apical muscular ventricular septal defect was closed with an ivalon patch (Prof. C. N. Barnard). When reviewed 7 months later, she had gained 7 lb. in weight and her effort tolerance had improved. The abnormal cardiac signs had disappeared, the heart size was normal, and the pulmonary plethora was much less obvious on X-ray. Her subsequent progress has been excellent.

Case 2

A 6-year-old English girl was admitted to the infectious diseases unit of St Ann's Hospital, suffering from scarlet fever. Apart from a congenital malformation of the left hand she had been quite well, though a cardiac murmur had been found at routine examination several months previously. She had been born of a normal pregnancy, during which her mother had neither taken thalidomide nor suffered from rubella or other viral infection. Her effort tolerance was normal. No relatives were known to suffer from malformations of the heart or limbs.

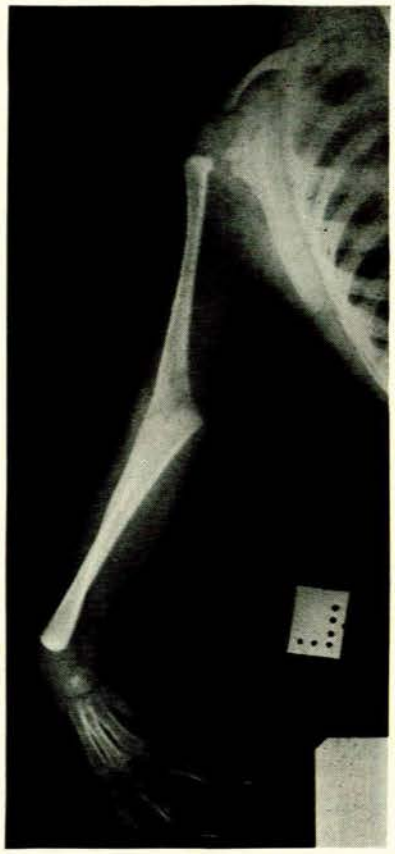

Fig. 3. X-ray showing skeletal abnormalities of right upper limb (case 1).

Examination revealed the typical features of scarlet fever, and the following cardiovascular and skeletal anomalies:

Cardiovascular system. There was marked bulging of the left anterior chest wall, with enlargement of the heart, and a heaving apical impulse in the fifth left interspace just beyond the midclavicular line. There was a harsh left lower parasternal pansystolic murmur (grade 5/6) and thrill, an accentuated pulmonic component of the second heart sound, and a short, rumbling, apical diastolic murmur.

Skeletal system. Apart from shortening of the neck, the only significant features were shortening of the left forearm, fixed adduction of the left hand at the wrist, and absence of the left thumb. The right upper limb was normal. Palm and fingerprint patterns were normal (Metropolitan Police). Radiological studies showed the presence of hemivertebrae and spina bifida in the neck. Plates of the arms (Fig. 4) show marked abnormalities on the left. The lower humerus was mis-shapen with a bony ridge on it. There was a rudimentary centre for the capitellum, and the

radius was absent. The lower ulna was deformed, and the trapezoid, centre for the scaphoid and the whole thumb were absent. The only abnormality in the right upper limb was that the thumb had an epiphysis at its head as well as at its base.

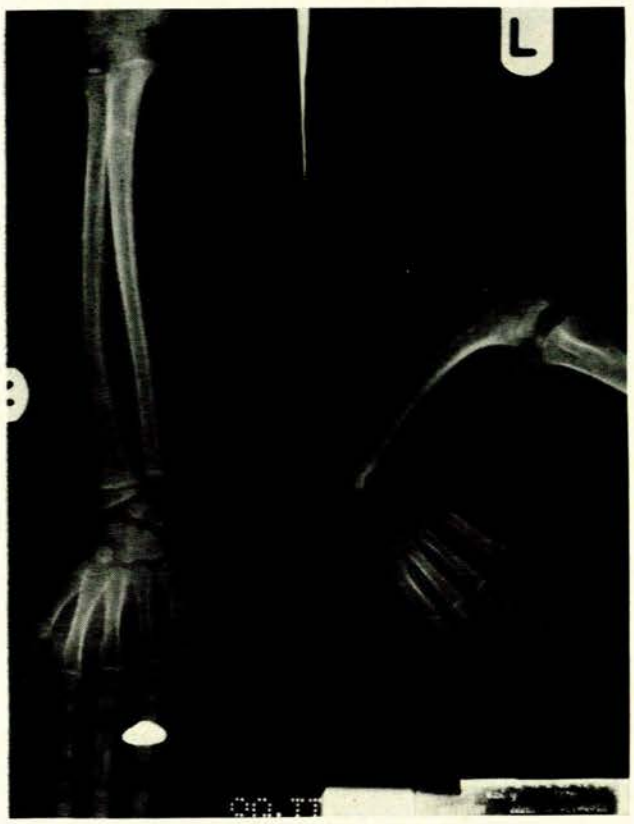

Fig. 4. X-rays of upper limbs (case 2) showing virtually normal structures on right, and absence of radius and thumb, and deformed ulna and lower humerus, on left.

Cardiac investigations. Radiologically and on the electrocardiogram there was evidence of biventricular hypertrophy.

Chromosome studies have not been carried out.

After she had recovered from scarlet fever she was discharged and referred back to a paediatric cardiac centre for further investigation. The signs are considered to indicate the presence of a ventricular septal defect with a large left-to-right shunt, and closely resemble those found in case 1.

DISCUSSION

The coexistence of congenital defects of the heart and upper limbs is of embryological and genetic interest. It strongly suggests an effect expressing itself at about the fifth week of embryogenesis, at the time when the upper limb and heart are differentiating. Thalidomide could certainly exert such an action,[11] though this is unusual, and there is nothing to suggest that the mothers took it during their pregnancies.

In considering heritable or congenital disorders of this kind, one must first exclude several generalized disease processes. In Marfan's syndrome, arachnodactyly may occur together with aortic arch abnormalities, but these are due to the underlying biochemical disturbance. Likewise, in major chromosomal aberrations, e.g. Down's and Turner's syndromes, if there are cardiac and upper limb defects they will be among the other more characteristic features of the disorders. Once, as in the present cases, these have been excluded, a more specific upper limb-cardiovascular syndrome becomes the likely diagnosis.

The type of upper limb and cardiac defects in these two cases are in keeping with those previously reported; the involvement of each system may be quite variable.[6] Presumably the embryopathic changes occur at the same stage of foetal development, viz. the 4th - 6th weeks. Indeed, the present cases fit well with the description of ventriculoradial dysplasia,[12] which may be one of a number of separate mutations that may express themselves at this time. Radial rather than ulnar abnormalities tend to predominate in patients with congenital heart disease and upper limb defects;[13] such cases may also have anomalies of other parts of the skeleton (as in the cervical spine in case 2), as well as the renal, pulmonary, haematological and alimentary systems. Case 1 was anaemic during infancy, but responded to iron, and there has been nothing to suggest marrow hypoplasia such as occurs in Fanconi's anaemia, in which anomalies of the upper limbs are also found. Indeed, a case of the latter disorder has been reported together with a ventricular septal defect and absence of both radii.[14] Although one cannot exclude the possibility that Fanconi's anaemia may become apparent as she grows older, this seems remote, especially as she—like other cases of the upper limb-cardiovascular syndrome—does not show the chromosomal breakage so frequently found in Fanconi's anaemia, and in that disease apparently associated with a tendency to develop leukaemia.[15]

In these syndromes it is always the upper and never the lower limbs that are affected, presumably because of the later differentiation of the latter, after the septa have closed.[5] We have not encountered reports of involvement of only one upper limb, as in case 2. Chromosomal abnormalities have not generally been found in this syndrome[7] —these are in any case not to be expected with dominant traits[5]—although an abnormality in pair 16, consisting of a constriction in the short arm of this chromosome, producing a bar-like satellite, has been reported.[9] In case 1 this aberration was not found. Dermatoglyphic abnormalities, which have been reported in association with ventricular septal defect and which are believed to represent differentiation disturbances occurring around the 7th week (there is some overlap with the time of ventricular septal closure),[16] are thought by most workers to be due to the underlying skeletal defects.[7,9]

Although he does not mention associated cardiac anomalies, Berry[17] has stressed the value of examination of the hand as a clue to the presence of systemic disorders. The finding of upper limb defects in a neonate should alert the physician to the possibility of a congenital cardiac lesion that may require further evaluation. Whether sporadic cases are phenocopies or are due to mutations capable of leading to dominant hereditary transmission will be determined by careful follow-up of patients such as those we have described.

SUMMARY

Some cases of congenital cardiac disease may be associated with upper limb defects, and this is believed to be due to an adverse stimulus operating between the 4th and 6th weeks of foetal life. Two cases of ventricular septal defect with dysplasia mainly affecting the radii are presented, and the clinical and genetic implications are discussed.

We wish to thank Dr G. D. W. McKendrick, under whose care she was admitted, for permitting us to publish case 2.

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