Two brothers with heart defects and limb shortening: case reports and review

W Reardon, J Hurst, T I Farag, C Hall, M Baraitser

Abstract
Two male Arab sibs are reported with congenital heart disease and skeletal malformations. Other published case reports sharing some features in common with these brothers are considered. However, clinical and radiological features in these boys are distinct enough to represent a new cardio-skeletal syndrome.

Cardioskeletal malformations may occur together in a number of recognisable syndromes. The best known of these are cardiac defects in association with proportional short stature in Noonan syndrome, and upper limb malformations occurring with congenital heart defects in the Holt-Oram syndrome. Few other recognisable syndromes combine a congenital heart defect with limb shortening. This report describes two brothers, offspring of consanguineous parents, in whom the predominant clinical features are abnormalities of the heart and skeleton. The combination of the anomalies observed has not been seen in a previously recognised syndrome.

Case reports
The pedigree is shown in fig 1. The parents were healthy, Kuwaiti first cousins (III-1 and III-2). The first pregnancy resulted in a late intrauterine death and a stillborn male infant was delivered. Congenital malformation was not noted in this infant and necropsy was not performed.

Case IV-2 was born at 39 weeks' gestation by spontaneous vaginal delivery. Owing to maternal anxiety regarding paucity of fetal movements, an ultrasound scan was performed at 26 weeks' gestation. Biparietal diameter was appropriate to gestational age but significant shortening of the femora and humeri was detected. Furthermore, the vertebrae were felt to be short and broad. A fetal bradycardia was noted, but heart rhythm was regular.

Birth weight was 3100 g (25th centile), head circumference 34 cm (25th to 50th centile), and length 42 cm (<3rd centile). The chest was thought to be narrow and all limbs were noted to be short. In view of continuing central cyanosis, a cardiac echogram was performed which showed gross hypoplasia of the right ventricle and tricuspid valve, with a large atrial septal defect, pulmonary atresia, and a cleft mitral valve. The infant died on the second day of life.

The third pregnancy ended in a first trimester spontaneous abortion.

Case IV-4 was born at term. Ultrasound scans at 13...
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Figure 2  Patient IV·4. Note the limb shortening.

Figure 3  Lateral spine radiograph with coronal clefts throughout the dorsal spine.

Figure 4  AP chest radiograph showing narrow thorax with large anterior ends of 6th to 8th ribs, and marked cardiac enlargement with pulmonary plethora.

and 22 weeks' gestation detected no abnormality but when repeated at 30 weeks shortening of all limbs was detected. Birth weight was 3000 g (25th centile). Limb shortening was evident (fig 2). When reviewed at 3 months of age a heart murmur and clinical evidence of cardiac failure were noted and he was referred for investigation. On admission, weight was on the 10th centile, head circumference on the 10th centile, and length well below the 3rd centile. Clinical examination showed a narrow chest. Cardiac investigations showed a ventricular septal defect and an atrial septal defect (secundum type). These defects
were subsequently closed at surgery, when the atrio-
ventricular valves were felt to be normal.

Skeletal x ray examination at the age of 5 months
showed mild thoracolumbar kyphosis and coronal
clefts extending through the dorsal and lumbar
vertebrae (fig 3). Chest x ray confirmed the clinical
impression of a narrow thorax and showed prominence
of the anterior ends of the sixth, seventh, and eighth
ribs as well as cardiac enlargement with pulmonary
plethora (fig 4). The long bones were shortened with
metaphyseal flaring (figs 5 and 6).

The femoral necks were broad, with prominent
lesser trochanters (fig 7). Bone maturation was
retarded at the knee but advanced at the wrist with
three carpal centres ossified. Chromosomes were
normal as were parental chromosomes, performed
with G banding techniques. This infant has since died
of cardiac complications.

Discussion

The critical clinical features in these brothers were
disproportionate short stature, owing to a mainly
rhizomelic limb shortening, and congenital heart
disease. A number of authors have documented cases
which fit these broad criteria and these will now be
considered.

Urbach et al\(^1\) reported an Arab baby with cardio-
skeletal anomalies, who was the offspring of a
consanguineous marriage. Two dead sibs probably
had the same condition. The clinical features in this
case were microcephaly, elbow flexion contractures,
severe psychomotor retardation, and pulmonary
stenosis. By contrast, microcephaly, contractures, or
retardation were not observed in our cases and the
cardiac malformations did not include pulmonary
stenosis (see table 1 for comparison of clinical
features). Radiological features in the case of Urbach
et al\(^1\) were a very distinctive upper limb rhizomelia
and flared epiphyses, platyspondyly, and bifid distal
phalanx of the thumb. The femora were of normal
length. As seen in table 2, these radiological features
differ substantially from those noted in the subject of
this report.

Barrow and Fitzsimmons\(^2\) described a male child
with severe cyanotic congenital heart disease owing to a single ventricle and truncus arteriosus. Rhizomelic short stature, particularly of the upper limbs, was also observed in this child. Unlike the cases we describe, marked facial dysmorphism was present in this child, with a very prominent nasal bridge and sloping forehead. The nature of the cardiac lesion was also substantially different from the cases we describe (table 1).

Sedaghatian described three Iranian sibs with rhizomelic limb shortening and platyspondyly. A further sib pair, also of Iranian extraction, was subsequently reported by Opitz et al. These children all died early in neonatal life of severe respiratory and metabolic abnormalities comprising severe respiratory acidosis, hypocalcaemia, and raised alkaline phosphatase levels, probably of renal origin. Necropsy showed no evidence of a cardiac lesion (table 1). While case IV-2 of the current report died in the neonatal period, this was almost certainly because of cardiac complications. With regard to radiological features, Sedaghatian syndrome also differs from the present report in that, although rhizomelia is common to both conditions, Sedaghatian syndrome patients have very irregular metaphyseal splaying at the knees and ankles not observed in the condition we describe. Furthermore, unlike our patients, coronal clefting was not seen in Sedaghatian syndrome patients (table 2).

Although Verloove et al described a condition with rhizomelia and congenital heart disease, that condition also involved cleft lip, bilobular lungs, and oligopoly-syndactyly, features not observed in the condition we describe.

The report which approximates most closely to the cases we describe is that of Kozlowski et al. Two half sibs were reported. Unlike our cases, both children had talipes equinovarus. Cardiac anomalies consisted of thickening of the left atrium, mitral, and tricuspid valves in case I and tricuspid incompetence and pulmonary hypertension in case II. Intracardiac shunts were excluded in both these cases whereas intracardiac shunts were cardinal clinical features of both cases in the present report (table 1).

Radiologically too, our cases differ from those of Kozlowski et al. Although coronal clefting of the vertebral bodies and limb shortening are features common to both reports, some essential differences are also observed. The patients in the report of Kozlowski et al had bifid distal humeral ends and radial subluxation at the elbow joint. Some metaphyseal flaring of the humeri and femora was seen in our patients (figs 4 and 5), but the bifid distal humeral ends, so characteristic of the Kozlowski report, were absent and the radii in our patient were not dislocated (table 2).

The clinical features in the sibs we describe were mainly rhizomelic limb shortening and congenital heart disease. These features, combined with radiological signs of coronal clefting of the vertebrae with shortening and metaphyseal flaring of the limbs, have not been previously described. Although radiological data on case IV-2 are unavailable, the clinical similarities between these brothers are compelling. That they shared the same condition is further supported by the ultrasonic diagnosis of short limbs made in both cases early in the third trimester. In view of the parental consanguinity, it seems likely that this report represents a new autosomal recessive condition. It is difficult to evaluate parental consan-
### Table 1  Comparison of clinical features observed in the reports discussed.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Short stature &lt;3rd centile</td>
<td>+</td>
</tr>
<tr>
<td>Limb shortening</td>
<td>Rhizomelic Pulmonary stenosis</td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>Included</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>Depressed nasal bridge</td>
</tr>
<tr>
<td>Other features</td>
<td>Microcephaly + motor and mental retardation</td>
</tr>
</tbody>
</table>

### Table 2  Comparison of radiological features observed in the reports discussed.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Limb</td>
<td>Rhizomelia of humeri only + flared epiphyses</td>
</tr>
<tr>
<td>Other</td>
<td>Bifid distal phalanx of thumb</td>
</tr>
</tbody>
</table>
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Consanguinity in this case as the inbreeding coefficient in the Middle East is high. However, the occurrence of a rare syndrome in two brothers suggests that this is a genetically determined condition, the mechanism of inheritance awaiting further reports.

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