Prenatal ultrasound diagnosis of the Holt-Oram syndrome

J. T. J. BRONS*, H. P. VAN GEIJN*, J. W. WLADIMIROFF†, J. J. VAN DER HARTEN‡,
M. L. KWEE§, M. SOBOTKA-PLOJHAR|| AND N. F. TH. ARTS*

*Department of Obstetrics and Gynaecology, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands; †Department of Obstetrics and Gynaecology, University Hospital Dijkzigt, Rotterdam, The Netherlands; ‡Department of Pathology, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands; §Department of Clinical Genetics, Vrije Universiteit, Amsterdam, The Netherlands; ||Department of Pediatric Cardiology, Vrije Universiteit, Amsterdam, The Netherlands

SUMMARY

The Holt–Oram syndrome is an autosomal dominant disorder consisting of a congenital heart defect in combination with characteristic upper limb abnormalities. This report presents the ultrasonographic follow-up of two fetuses at risk for the Holt–Oram syndrome. In the first fetus, the existence of Holt–Oram syndrome was suspected at 22 weeks of gestation; a ventricular septal defect, an atrial septal defect, and a minor skeletal defect were found. In the second fetus, no structural abnormalities were discovered until the 30th week, when a small atrial septal defect was detected. In both pregnancies, it was possible to exclude early in gestation the more severe forms of the Holt–Oram syndrome.

KEY WORDS Holt–Oram syndrome Prenatal diagnosis Diagnostic ultrasound

INTRODUCTION

In 1960, Holt and Oram first described a syndrome of congenital heart malformations and upper limb deformities which followed an autosomal pattern of inheritance (Holt and Oram, 1960). Subsequent family studies have confirmed the autosomal dominant transmission of this syndrome with complete penetrance (Gladstone and Sybert, 1982). There is a variable expression of both the skeletal and cardiac defects (Kaufman et al., 1974; Silver et al., 1972; Smith et al., 1979).

The skeletal abnormalities range from severe phocomelia to minor abnormalities such as deformed carpal bone, evident only by means of radiography. The following structures of the skeleton can be affected (Ponazski et al., 1970): thumbs (hypoplastic thenar eminences, triphalangeal, clinodactyly, syndactyly, absent first metacarpals, absent thumbs), fifth finger (short middle phalanx, clinodactyly), carpal bones (deformed or extra carpalars), shoulders (deformed scapula and/or clavicle, deformed head of the humerus, accessory bones), radius and ulna (partially or completely missing, synostosis), and sternum (deformed). There is a striking asymmetry of skeletal involvement, often with the left side more affected than the right side (Smith et al., 1979). To date, abnormalities of the lower extremities have not been described in the Holt–Oram syndrome. The cardiac abnormalities range from a com-
bination of severe atrial septal defect, ventricular septal defect, and pulmonic stenosis, to no heart defect at all. Other possible cardiac manifestations are mitral valve prolapse, anomalous pulmonary venous return, and conduction defects (Smith et al., 1979).

This report presents the ultrasonographic follow-up of two subsequent pregnancies of a woman who is herself affected by the Holt–Oram syndrome.

CASE REPORT

Mrs A (II-2, Figure 1) was born in 1946; she was an only child. At the age of 10 years, she had cardiac surgery for an atrial septal defect. There were no apparent skeletal abnormalities, but at the age of 37, at a genetic consultation, decreased pronation and supination of her forearms was found. Furthermore, she had slight anterior rotation of both shoulders and slight clinodactyly of the left and right fifth fingers. Her thumbs were normal (see Figure 2). Her mother (I-2, Figure 1)

Figure 1. Pedigree of family A with Holt–Oram syndrome. (Mrs A = II-2)

Figure 2. Hands of Mrs A. Normal thumbs, slight clinodactyly of the fifth fingers
also had decreased pronation and supination of her forearms and slight clinodactyly of the fifth fingers.

Her father did not have any signs of limb or heart abnormalities. Mrs A's husband did not have any signs of a limb or heart anomaly, and his family history was uneventful. There was no consanguinity between them.

Mrs A has had nine pregnancies. A summary of all nine pregnancies is presented in Table 1. Although the first two children were affected with the Holt–Oram syndrome, this particular syndrome was not diagnosed until after the third child was born in 1973. The couple were then informed of the likelihood of this syndrome and the recurrence risk of 50 per cent.

Between 1973 and 1983, she had four more pregnancies. Three pregnancies ended in a miscarriage. In 1977, a fourth child was born with manifestations of the Holt–Oram syndrome. In 1983, at the beginning of her eighth pregnancy, she visited the Department of Clinical Genetics (Vrije Universiteit, Amsterdam), mainly to enquire about the possibilities of prenatal diagnosis. She was informed that the only possibility for prenatal diagnosis was real-time ultrasonography, since there are no known concomitant chromosomal abnormalities or metabolic disturbances in the Holt–Oram syndrome.

The first ultrasonographic evaluation was at 14 weeks of gestation; a fetus with a normal biparietal diameter and a normal femur length for gestational age was visualized. A humerus, an ulna–radius complex, and a hand were seen on either side of the body; the posture of the hands appeared to be normal. In the course
<table>
<thead>
<tr>
<th>No. of pedigree</th>
<th>Birth year</th>
<th>Gestational age at birth (weeks)</th>
<th>Birth weight (g)</th>
<th>Sex and chromosomes</th>
<th>Upper limb anomalies</th>
<th>Heart defect</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-1</td>
<td>1971</td>
<td>40</td>
<td>3490</td>
<td>male/—</td>
<td>Finger-like thumbs</td>
<td>ASD, VSD pulmonic stenosis</td>
<td>Died at the age of 1 month, following cardiac surgery (see figure 3)</td>
</tr>
<tr>
<td>III-2</td>
<td>1972</td>
<td>19</td>
<td>45</td>
<td>male/—</td>
<td>Severe phocomelia&lt;br&gt;Right: Absence of radius and ulna. Hand consisting of 3 metacarpals and 3 digits, directly linked to the humerus. Left: Absence of humerus, radius, and ulna. Hand consisting of 2 metacarpals and 2 digits, directly linked to the shoulder. Scapula hypoplastic&lt;br&gt;Right: Syndactyly of the first and second digit; first metacarpal missing. Left: Finger-like thumb</td>
<td>No abnormalities</td>
<td>Stillborn</td>
</tr>
<tr>
<td>III-3</td>
<td>1973</td>
<td>40</td>
<td>4000</td>
<td>male/46 XY</td>
<td>ASD</td>
<td>Cardiac surgery at the age of 5 years; developing well</td>
<td></td>
</tr>
<tr>
<td>III-4</td>
<td>1977</td>
<td>40</td>
<td>3500</td>
<td>male/46 XY</td>
<td>ASD</td>
<td>Cardiac surgery at the age of 5 years; developing well</td>
<td></td>
</tr>
<tr>
<td>III-8</td>
<td>1983</td>
<td>40</td>
<td>3480</td>
<td>male/46 XY</td>
<td>Finger-like thumbs</td>
<td>ASD, VSD</td>
<td></td>
</tr>
<tr>
<td>III-9</td>
<td>1985</td>
<td>39</td>
<td>3850</td>
<td>male/46 XY</td>
<td>No evident skeletal abnormalities at birth</td>
<td>ASD</td>
<td></td>
</tr>
</tbody>
</table>
of the pregnancy, the growth curves of both humeri followed the 50th percentile, the ulna–radius complex the 25th percentile, and the femur the 75th percentile. The growth curves of Jeanty and Romero (1984) were applied. At 22 weeks of gestation, the left radius was suspected to be 4 mm shorter than the right radius, but the posture of the left hand again appeared to be normal. In addition, a ventricular and an atrial septal defect were found.

At a gestational age of 40 weeks, a male infant was born in good condition with a birth weight of 3480 g. Both arms had a normal appearance, and X-ray examination did not confirm the suspected slight shortening of the left radius. The only expression of a skeletal abnormality was the existence of finger-like thumbs. The antenatally suspected ventricular and atrial septal defects were confirmed by echocardiography and heart catheterization with angiography. The infant had cardiac surgery at the age of 9 months and is developing well.

In 1985, during her ninth pregnancy, the first ultrasonographic evaluation was at 13 weeks of gestation. A fetus with a normal biparietal diameter and femur length for gestational age was seen. On both sides of the fetal body, a normal humerus, an ulna–radius complex, and a hand were observed, with normal posture of the hand. Throughout the pregnancy, the growth parameters of the humerus, ulna–radius complex, and femur followed the 50th percentile (according to Jeanty and Romero (1984). At 20 and 24 weeks of gestation, no structural abnormalities of the heart were seen, but at 30 weeks a small atrial septal defect was discovered. At 39 weeks of gestation, a male infant was born in good condition, birth weight 3850 g. The infant had no signs of a skeletal abnormality. The antenatally suspected small atrial septal defect was confirmed by echocardiography. At the age of 1 year, heart sounds were normal and a spontaneous closure of the lesion was confirmed by echocardiography.

DISCUSSION

Congenital heart disease occurs in about 1 per cent of births. In the majority of cases, the etiology is unknown and is most likely of multifactorial origin. According to Campbell (1959) and Wood (1958), the recurrence risk for sibs of a proband with an isolated congenital heart disease is 2–5 per cent.

Congenital heart disease can be a part of many syndromes. One of them is the Holt–Oram syndrome. In the case of a congenital heart defect in association with upper limb deformities, apart from the Holt–Oram syndrome, the following conditions must be considered (Kaufman et al., 1974): chromosomal disorders such as trisomy 13 and trisomy 18, some autosomal recessive disorders, i.e., Fanconi anaemia and the thrombocytopenia absent radius syndrome (TAR syndrome), and the sporadic VACTERL association and Aase syndrome.

The following aspects of the Holt–Oram syndrome, described by several authors, are well illustrated by the case presented here:

(a) the variable expression (Kaufman et al., 1974);
(b) the absence of a correlation between the severity of the affected parent and the affected offspring (Gladstone and Sybert, 1982);
(c) the absence of a correlation between the severity of the cardiac defect and
the skeletal abnormalities in a given individual (Gladstone and Sybert, 1982); e.g., the second child had severe phocomelia but no heart defect (see Figure 2); the left side being more affected than the right side;
(d) members of a family with Holt–Oram syndrome who only have skeletal defects (e.g., the mother of Mrs A; I-2) must be considered as having the Holt–Oram syndrome, since they can have offspring affected with both cardiac and skeletal defects (Smith et al., 1979).

It is very probable that the last child (III-9) is also affected by the Holt–Oram syndrome, although only a small atrial septal defect was found and evidence for an upper limb deformity was absent on physical examination. X-ray examination of the wrists, at the age of 17–19 years, when ossification is complete, will provide valuable information. Poznanski et al. (1970) found carpal anomalies in their series in all wrists of people affected by the Holt–Oram syndrome. These carpal anomalies are distinctive and may be present even when the digits are normal. Scaphoid malformation is the most common anomaly.

Ultrasonographic evaluation of normal fetal limb growth and the detection of skeletal dysplasias was first published in 1980 by Queenan et al. Reports on the prenatal identification of normal cardiac structure by real-time ultrasonography appeared in the late 1970s (Lee et al., 1977; Ianniruberto et al., 1977; Baars et al., 1977; Wladimiroff et al., 1979). Prenatal ultrasonographic detection of the Holt–Oram syndrome has only recently been described by Muller et al. (1985).

With regard to the ultrasonographic evaluation of skeletal structures, in our experience it appears that the ulna–radius complex is the most difficult structure to measure. Because of pronation and supination, the ulna and radius are seldomly visualized parallel in the second trimester of pregnancy. In the case of supination or pronation of the hand, parts of the ulna and radius are projected on top of each other and the mistake is easily made that one of the two bones is too short. We feel that the best time to evaluate the ulna–radius complex is between 13 and 16 weeks of gestation because then the extremities are moving freely in a relatively large amniotic fluid compartment. In that period of gestation, the radius and ulna can almost always be visualized parallel on the ultrasound screen.

The posture of the hands should be evaluated during ultrasonography in fetuses at risk for the Holt–Oram syndrome. In most cases of radial hypoplasia, there is a radial deviation of the hand, causing a clubhand (see pregnancy 4 in Table 1). A normal posture of the hand is an important and reassuring finding.

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REFERENCES

HOLT–ORAM SYNDROME

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