The antenatal ultrasonographic detection of the Holt-Oram syndrome

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Summary

The Holt-Oram syndrome is an autosomal dominant disease with 100% penetrance. No correlation exists between the maternal clinical expression and that of the affected offspring. The syndrome includes a wide range of cardiac and skeletal malformations. Real-time ultrasound, with a detailed study of the fetal heart and skeletal system, can play a crucial role in the counselling of affected pregnant women. This study describes the ultrasonographic findings of 2 affected fetuses at risk (at 34 and 14 weeks' gestational age). Ultrasonography detected and correctly estimated the severity of the cardiac and skeletal expressions.

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The Holt-Oram syndrome of skeletal and cardiovascular abnormalities was first described by Holt and Oram in 1960.[1] The clinical expression may vary widely. Cardiovascular malformations include atrial septal defect (ASD), ventricular septal defect (VSD), mitral valve prolapse, patent ductus arteriosus (PDA), anomalous pulmonary venous return and conduction defects.[2-4] Skeletal abnormalities also show a wide variation from shoulder defects to phocomelia, digitalized or absent thumbs, syndactyly, clinodactyly and hypoplastic or absent first metacarpals or radii. Articulation defects could manifest as impaired forearm supination, elbow extension and thumb apposition.[2,4,5]

This upper-limb cardiovascular syndrome is an autosomal dominant disease with 100% penetrance. A recent study found no significant maternal influence on the severity of the expression in affected offspring.[2]

With modern high-resolution real-time ultrasonography it is possible to perform a detailed antenatal study of the fetus, including the fetal heart and skeletal system. Ultrasound studies are crucial in the genetic counselling of couples with a family history of this disease.

Two pregnancies of an affected mother, where ultrasound detected and could determine the severity of the defect in the fetuses, are described. The ultrasound examinations were done with a Siemens Pho-Sonic series 2000 linear array scanner. A detailed study of the fetal skeleton included measurements of the long bones and biparietal diameter (BPD), visualization of the metacarpals and the metatarsals, as well as assessment of limb movement. The visceral organs were studied with special emphasis on the heart, as previously described.[6]

Case report

The patient, her 2 sisters and their mother were all known to have the Holt-Oram syndrome, with ASDs and fingerized thumbs. These defects had been surgically corrected. In her first pregnancy this 22-year-old patient was referred at 34 weeks gestational age for a detailed sonographic study. Her gynaecologist had, on routine ultrasound examination, detected polyhydramnios and had experienced difficulty in demonstrating the fetal arms.

Our examination showed a single fetus of unstable lie due to polyhydramnios. The BPD of 84 mm confirmed a mean gestational age of 34 weeks. The lengths of the femora, tibiae, fibulae and humeri correlated with the BPD and the limbs moved normally. However, the radii and ulnae could not be separately demonstrated. Only one forearm bone on each side could be seen, turned medially towards the fetal body. Four fingers were noted on the right hand and 3 on the left (Fig. 1). The echocardiographic study, though made difficult by the excess amniotic fluid, showed apparently normal atria and ventricles, mitral, tricuspid and aortic valves, and a normal foramen ovale. The interventricular septum appeared abnormal, and a VSD was suspected. The fetal heart rate was within normal limits. The rest of the fetal organs appeared normal. A diagnosis of Holt-Oram syndrome with absent radii, missing digits and a VSD was made.

The patient went into premature labour and was delivered of a 1 280 g male infant, who had typical Madelung deformities (Fig. 1). A radiograph confirmed the absent radii, absent thumbs on both hands and absent fourth digit on the left hand (Fig. 2). The baby developed respiratory distress and died 8 days later of pneumonia. Autopsy showed an ASD, VSD and PDA, as well as necrotizing enterocolitis and a tracheo-oesophageal fistula.

The same patient was seen again 6 months later. She was 14 weeks pregnant by dates and had requested an ultrasound examination. This showed a fetus with a BPD of 29 mm, consistent with a gestational age of 14 - 15 weeks. The femora, tibiae, fibulae and humeri could be measured and movement appeared normal. The left forearm was deviated towards the fetal body, the radius was absent and only three fingers could be identified (Fig. 3). On the right the radius was also absent, with the elbow in fixed extension. Again, three fingers were demonstrated (Fig. 4). The other fetal organs appeared normal, but it was too early for detailed cardiac evaluation.

The ultrasound examination was repeated at 18 weeks' gestation, the skeletal abnormalities remaining constant. The echocardiographic examination showed four cardiac chambers and normal mitral, tricuspid, and aortic valves. The interventricular septum could not be demonstrated. This ultrasound examination confirmed the diagnosis of Holt-Oram syndrome; the skeletal expression being bilateral absent radii, fixed extension of the right elbow and two digits absent on both hands; the cardiac lesion was thought to be a large VSD.

In view of the family history and the severity of the condition in this fetus, the parents elected termination of the

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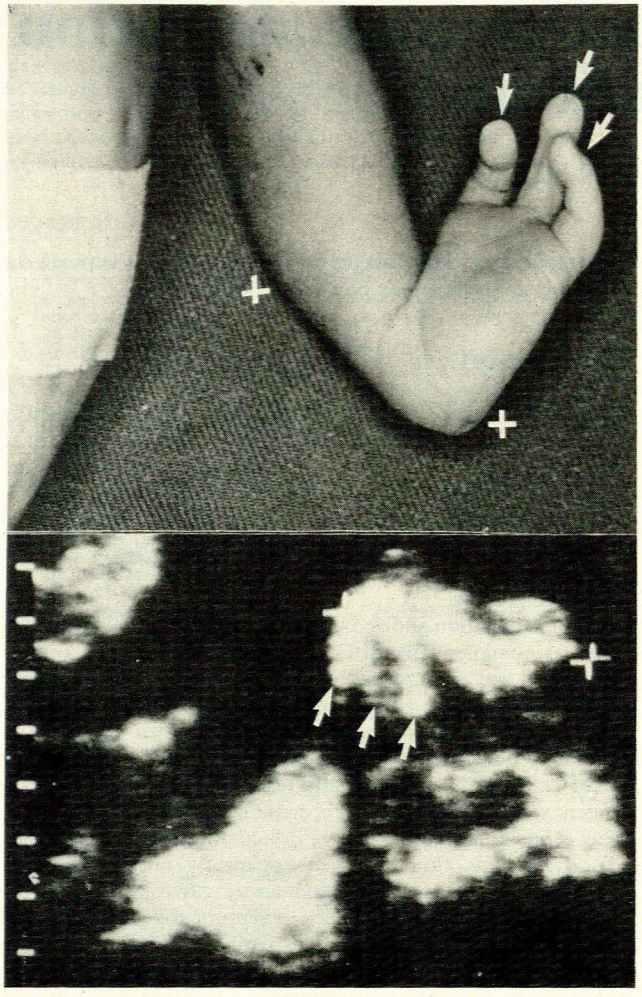

Fig. 1. Left forearm and hand. The calipers on the sonogram mark the proximal end of the abnormal forearm and the upturned hand. The arrows indicate the three digits.

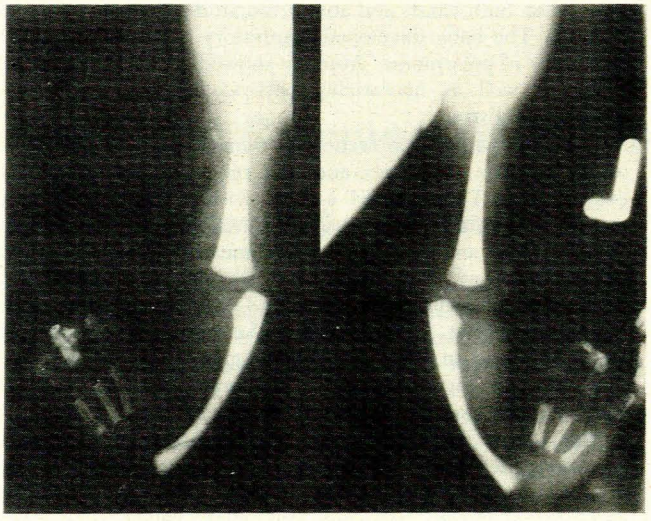

Fig. 2. Radiographs confirmed the absent radii and digits.

pregnancy. A male fetus weighing 200 g was aborted. Radiography confirmed the absent radii and fingers (Fig. 5). At autopsy the heart revealed normal valves, a PDA and a large VSD.

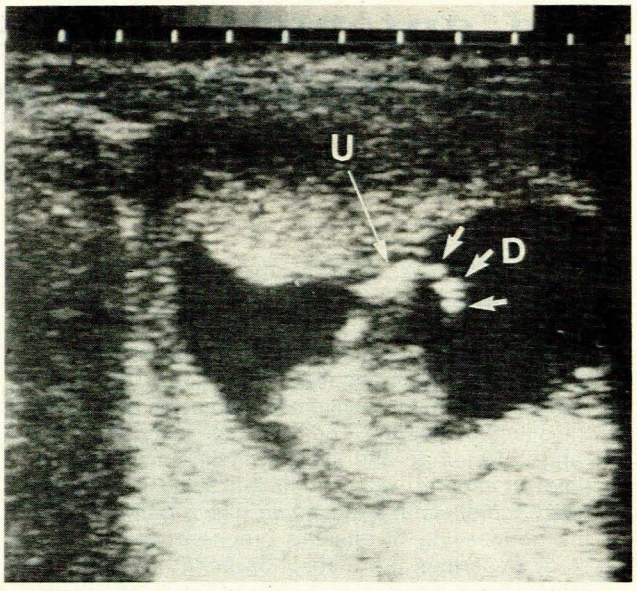

Fig. 3. A sonogram at 14 weeks shows a single left forearm bone, the ulna (U), with only three digits (D), turned medially (Madelung deformity).

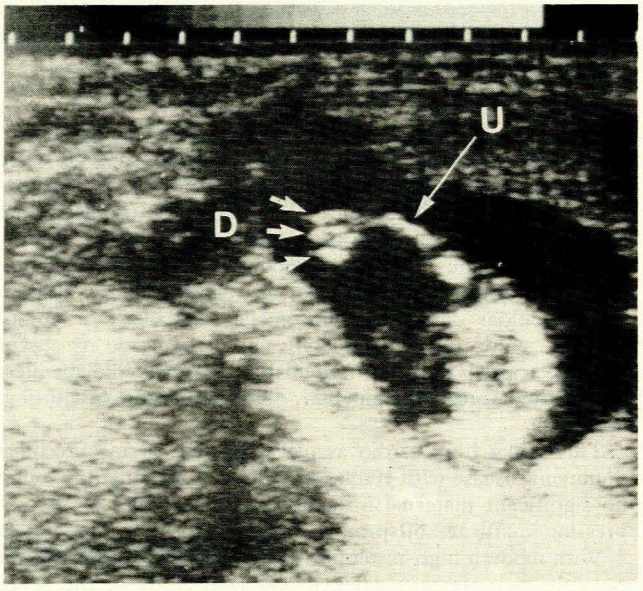

Fig. 4. The right forearm shows the ulna (U) and three digits (D). Using real-time mode, no flexion of the elbow joint could be seen.

Discussion

The pathogenesis of the Holt-Oram syndrome is uncertain. The upper limbs and the heart both undergo important structural development during the 4th and 5th weeks of embryonic life. It has been postulated that products of the mutant gene might interfere with normal differentiation of the heart and upper extremities.[7] However, many genes affect the differentiation of these structures and the genetic constitution of the individual will determine the exact degree of involvement. This theory evolved after the thalidomide tragedy, when it was found that children had similar defects (such as phocomelia and congenital heart disease) when their mothers had taken the drug during the 4th and 5th weeks of pregnancy.[7]

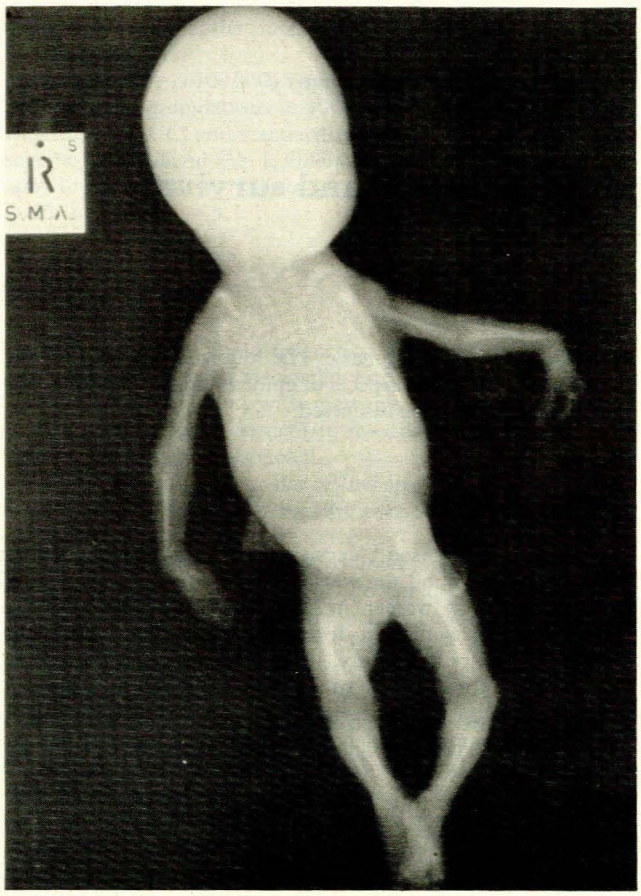

Fig. 5. The radiograph confirmed the absent radii and digits.

Smith *et al.*[3] suggested that a segmental defect in embryonic nerve supply from the 5th to the 8th cervical segments — especially the 6th cervical nerve — might cause these abnormalities. An alternative explanation could be a deficient fetal blood supply due to vascular hypoplasia of the upper limb. Hoyme *et al.*[8] found that in many instances of transverse limb reduction defects, and in sporadic cases of radial aplasia, an early gestational disruption of blood supply to the developing limb was present. This was, however, not found in cases of thrombocytopenia and absent radii syndrome (TAR syndrome).

There are other conditions with both cardiovascular and upper-limb defects from which the Holt-Oram syndrome must be differentiated. The most important ones which could cause confusion, especially on ultrasonic examination, are: chromosomal defects (trisomy 13, trisomy 18 and the 13q-syndrome), the TAR syndrome, Fanconi aplastic anaemia (both autosomal recessive diseases) and sporadic cases of the VATER association.[5]

When diagnosed early enough the chromosomal defects can be confirmed by an amniocentesis. Unless a positive family history is present, definitive antenatal diagnosis cannot be made in all instances.

Conclusion

This study has demonstrated that it might be possible to detect the presence of upper-limb syndromes as early as 14 weeks' gestation. The severity of limb involvement may be assessed by a detailed study of the long bones, including their measurements, number of bones and limb movement. Even digital defects can be detected.

Milder cases may be missed, but in families with a history of this condition the role of ultrasound is primarily to detect the more severely affected fetus. Counselling the parents can then be done on a rational basis.

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REFERENCES

1. Holt M, Oram S. Familial heart disease with skeletal malformations. *Br Heart J* 1960; **22:** 236-242.
2. Gladstone I jun, Sybert VP. The Holt-Oram syndrome: penetrance of the gene and lack of maternal effect. *Clin Genet* 1982; **21:** 98-103.
3. Smith AT, Sack GH jun, Taylor GJ. The Holt-Oram syndrome. *J Pediatr* 1979; **95:** 538-543.
4. Poznanski AK, Gall JC, Stern AM. Skeletal manifestations of the Holt-Oram syndrome. *Radiology* 1970; **94:** 45-53.
5. Kaufman RL, Rimoin DL, McAlister WH, Hartmann AF. Variable expression of the Holt-Oram syndrome. *Am J Dis Child* 1974; **127:** 21-25.
6. Muller L. Fetal echocardiography. *S Afr Med J* 1982; **62:** 796-797.
7. Lewis KB, Bruce RA, Baum D, Motulsky AG. The upper limb-cardiovascular syndrome. *JAMA* 1965; **193:** 1080-1086.
8. Hoyme HE, Van Allen MI, Jones KL. The vascular pathogenesis of some sporadically occuring limb defects. *Semin Perinatol* 1983; **7:** 299-306.