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Acardius in a Triplet Pregnancy: Cytogenetic and Morphological Profile

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Abstract. We describe a rare case of acardius in a triplet pregnancy terminated by Caesarean Section at 32 weeks gestation. Morphological and chromosomal abnormalities of the fetus as well as structural abnormalities of the placenta are presented. Cytogenetic analysis and examination of the single disc triplet placenta provide evidence for the two major theories of pathogenesis of acardius, the twin reversed arterial perfusion (TRAP) sequence and the genetic theory, which we believe are not necessarily mutually exclusive.

Key words: Acardius, Triplet pregnancy, Cytogenetic analysis.

INTRODUCTION

The acardiac fetus is a rare, severe, sporadic congenital anomaly associated with monozygotic twinning. Various incidence figures have been published. However, the generally accepted frequency is 1:34,600 births [1,5,6]. This is probably an underestimation of the true incidence owing to factors such as incorrect diagnosis or lethality [1,12]. Acardiac fetus is characterised by multiple defects of organogenesis. All cases have in common the absence of recognizable cardiac tissue and the maintenance of intrauterine viability by parasitic anastomosis of the circulation of the acardiac fetus to that of the normal cotwin.

We believe this report to be the first recorded demonstration of a chromosomal abnormality in a triplet acardius.

CASE REPORT

The proband was born at 32 weeks gestation to a 21 year old primigravida. Ultrasonographic examination had confirmed a triplet pregnancy at 18 weeks with one of the triplets showing absent fetal heart beats. It is of note that the triplet with the absent heart beats exhibited normal growth over this period during serial ultrasonography.

The patient remained hospitalised until she went into premature labour at 32 weeks when she was delivered by an emergency lower segment caesarean section as the presenting triplet was a footling breech. Three female infants were delivered. Triplets I and II were structurally normal and triplet III was a grossly malformed fresh stillbirth [Fig. 1].

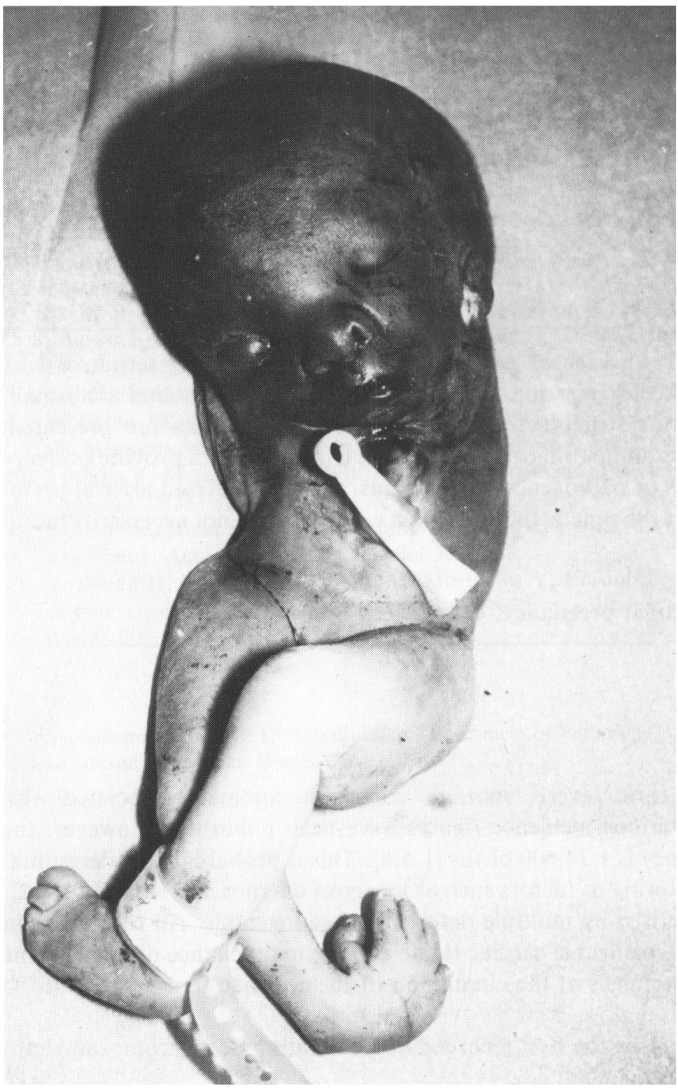

Fig. 1. Acardiac female infant showing multiple external anomalies, with preferential development of the lower half of the body.

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No positive family history was obtained. Triplet I and II required intubation at birth followed by ventilation because of respiratory distress syndrome. Ventilation was continued for 4 days when both infants were extubated.

Necropsy examination of the third infant disclosed multiple malformations including ocular agenesis and fusion of eyelids [Fig. 1]. The right ear was absent, the left ear was poorly developed. There was complete agenesis of the upper limbs, absence of heart, complete pulmonary agenesis and absent diaphragm, complete agenesis of liver and pancreas, hypoplasia of spleen, right renal agenesis and the gastrointestinal tract was represented by a short doubly blind-ending small intestine and a proximally blindended matrotated colon, with no evidence of oesophageal or gastric development. The lower half of the body and lower limbs were better developed than the upper half with preferential lower limb growth and bilateral talipes equinovarus. The brain showed hydrocephalus with aqueduct obstruction and stenosis of the foramen magnum. There was also hydrometrocolpos. Postmortem radiology of the infant showed multiple skeletal abnormalities. The arms, clavicles, scapulae, and sternum were absent. The spine showed scoliosis with marked shortening of the thoracic and cervical regions where multiple hemivertebrae and spina bifida were seen. Only 8 pairs of hypoplastic ribs were present.

Placenta

Examination of the single disc triplet placenta revealed a monochorionic triamniotic structure with a major arterial anastomosis between the single umbilical artery of the acardiac and one of the two umbilical arteries of cotriplet II allowing shunting of blood to the abnormal fetus. The respective cords were inserted on the fetal surface of the placenta, close to each other on either side of the dividing membrane, so that a short arterial connection between the two was readily appreciated [Fig. 2]. Air injection also revealed copious vein-to-vein anastomoses between all 3 of the triplets.

Cytogenetic Study

The liveborn cotriplets had completely normal 46XX, female karyotypes and chromosomal banding studies showed them to be identical. Both parents had normal karyotypes. Cytogenetic analysis of the acardius yielded a mosaic 4N (92) and 6N (138) hyperdiploid state [Fig. 3], although this was found in only a small number of lymphocytes obtained from a plexus of thin-walled vessels in the thoracic area of the acardius. The 4N mosaic could be regarded as a culture induced artefact, but the 6N hyperdiploid component was interpreted as a significant abnormality. Skin fibrolasts from the acardiac fetus failed to grow in culture.

DISCUSSION

There are two theories of the pathogenesis of the acardiac anomaly. The first, and most generally accepted theory is the twin reversed arterial perfusion (TRAP) sequence [1,2,12]. This theory holds that the malformations seen in the acardius sequence occur as a consequence of a major placental artery to artery anastomosis leading to reversal

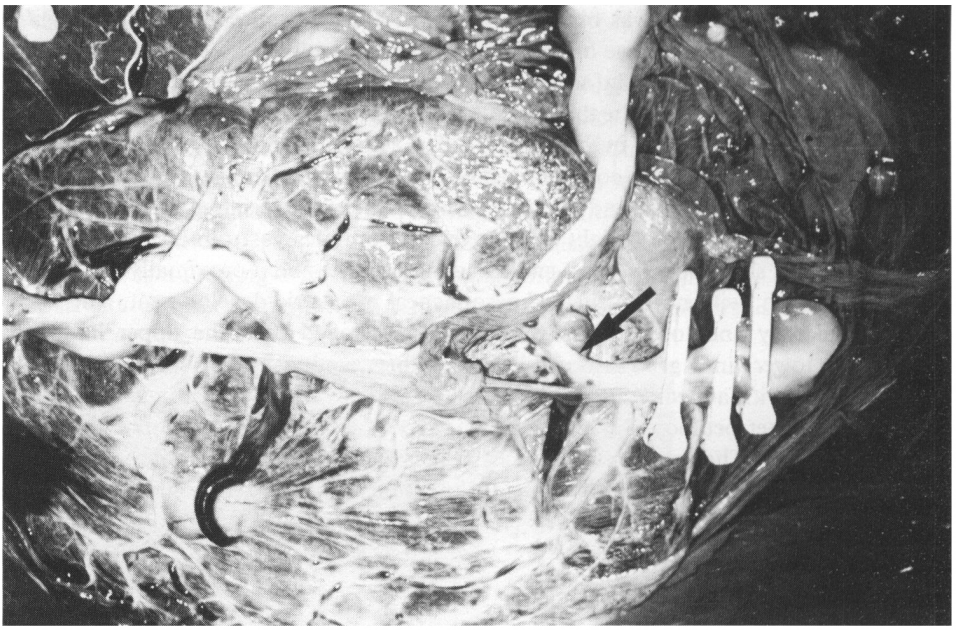

Fig. 2. The fetal surface of the monochorionic, triamniotic placenta shows direct anastomosis between the single umbilical artery of the cord of triplet III, with one of the umbilical arteries of the cord of triplet II (arrow). Anticipated V-V anastomoses were confirmed by an air injection technique.

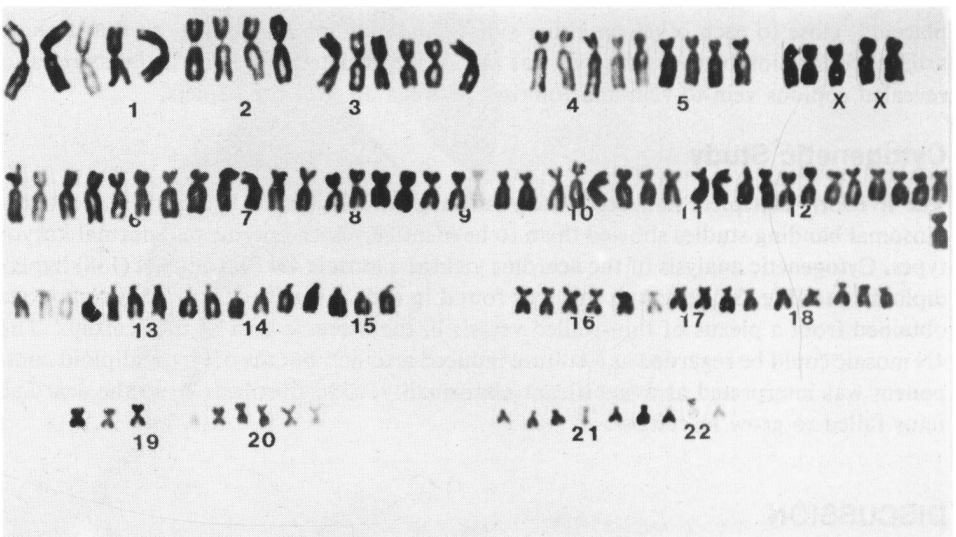

Fig. 3. Cytogenetic analysis of lymphocytes of triplet III shows a 6N hyperdiploid karyotype. This figure shows 118 mounted photographed chromoses matched as closely as possible from a 124 metaphase spread, regarded as a 6N hyperdiploid constitution with loss of some chromosomes. The 5 chromosomes at the end of line I are the sex chromosomes. There are clearly 5X chromosomes present. No Y chromosomes were found.

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of blood flow through the single umbilical artery of the acardiac fetus. Fig. 2 illustrates the TRAP sequence of events. The fundamental requirement is the development of placental arterial anastomosis between twins early in the first trimester. As artery-to-artery anastomosis often occurs in monochorionic placentas of normal twins, the TRAP theory therefore requires that some factor must cause early delayed development of one twin allowing the other twin to take over its circulation. Thus, the perfused twin becomes dependent on the pump twin for its blood supply. Inadequate perfusion with blood poor in oxygen and nutrients causes fetal malformation, often with selectively better development of the lower limbs and lower parts of the body at the expense of the cranial anatomy, as in our case.

The second, genetic theory [2,3,8,11] holds that a chromosomal abnormality is the primary aetiological event. The concept behind the genetic theory is that the acardius is a MZ twin with a severe, genetically determined defect including cardiac agenesis/regression, and that the normal cotwin maintains the *in-utero viability* of the acardius via a placental arterial shunt, this also representing a genetically determined anomaly. Evidence of chromosomal abnormalities in acardiac twins is recorded [2,3,8,11] but many acardiac infants are chromosomally normal while others have been untested. How one supposedly identical twin can exhibit such an abnormality, while the other is normal is explicable as follows. Although MZ twins are by implication genetically identical, the occurrence of MZ twins with different chromosome complements has been documented [7] and includes, for example, Downs Syndrome occurring in one twin while the other is normal. The best illustrated chromosomal study of an acardius is that of Bieber et al [3], who described a monochorionic twin pair, one of whom was a normal male infant while the other was a triploid XXX acardius. Chromosomal studies, isoenzyme and HLA typing of both parents and twins in this study showed that this particular case occurred by fertilization of an ovum and its diploid first polar body by separate sperms giving rise to a normal twin and a triploid monochorionic acardius. Thus, they convincingly demonstrated that the normal twin inherited a single HLA haplotype from each of its parents, whereas the acardius had inherited a single paternal and both maternal HLA haplotypes. Furthermore, as the inherited paternal HLA haplotypes were different in each twin, fertilization of the ovum and its first polar body by different sperms must have occurred. This was further confirmed by appropriate isoenzyme studies. Triploidy itself is a lethal genetic abnormality and again in this case, the acardius remained viable in utero by virtue of perfusion by the normal cotwin via an arterial shunt.

One of us (G M) [10], in a previous study showed that monochorionic twins, who are conventionally regarded as MZ [4,9], are not necessarily genetically identical. In this study, 12 sets of monochorionic, like-sex twins were tested for a range of major and minor blood group antigens. Nine sets of twins were found to be completely identical while 3 sets showed differences in their minor blood group antigen profiles. This is explicable by a somatic genetic mutation occurring in one twin soon after fertilization. The high frequency of its occurrence in this study is surprising. Scott and Ferguson-Smith [11] described 2 cases of acardiac monsters occurring in monozygous, diamniotic, monochorionic twin pregnancies. In one case, chromosome analysis of the acardius failed, while in the other case fibroblast cultures revealed G-Trisomy in the acardius whereas its cotwin had a normal karyotype.

CONCLUSION

Our case allows us to combine the two major theories of pathogenesis. The presence of a chromosomal defect or other constitutional abnormality of early embryogenesis in one fetus of a monochorionic multiple pregnancy may cause discordant development. In such a situation, the presence of a major placental arterial anastomosis may sustain the development of the defective embryo with cardiac agenesis and may also help to induce the additional morphological abnormalities associated with acardius.

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REFERENCES

1. Benirschke K, Harper VDR (1977): The acardiac anomaly. Teratology 16:311-316.
2. Benirschke K, Kim CK (1973): Multiple pregnancy. N Engl J Med 288:1276-1284.
3. Bieber FR, Nance WE, Morton CG, Brown JA, Redwine FO, Jordan RL, Mohanakumar T (1981): Genetic studies of an acardiac monster: evidence of polar body twinning in man. Science 213:775-777.
4. Fox H (1978): The placenta in multiple pregnancy. In Bennington JL (ed): Pathology of the placenta. London: WB Saunders.
5. Gilliam DL, Hendricks CH (1953): Holoacardius: Review of the literature and case report. Obstet Gynecol 2:647-653.
6. Kappleman MD (1944): Acardius amorphus. Am J Obstet Gynecol 47:412-416.
7. Lejeune J, Lafourcade J, Scharer K, et al (1962): Monozygotisme heterocaryote, jumeau normal et jumeau trisomique 21. CR Acad Sci 254:4404-4406.
8. Moore CA, Buehler BA, McManus BM, Harmon JP, Mirkin LD, Goldstein DJ (1987): Acephalus-acardia in twins with aneuploidy. Am J Med Genet Suppl 3:139-143.
9. Morison JE (1970): Multiple births. In Foetal and Neonatal Pathology. London: Butterworths.
10. Mortimer G (1987): Zygosity and placental structure in monochorionic twins. Acta Genet Med Gemellol 36:417-420.
11. Scott JM, Ferguson-Smith MA (1973): Hetero-Karyotypic monozygotic twins and the acardiac monster. J Obstet Gynaecol Brit Commonwealth 80:52-59.
12. Van Allen MI, Smith DW, Shepard TH (1983): Twin reversed arterial perfusion (TRAP) sequence: a study of 14 twin pregnancies with acardius. Semin Perinatol 7: 285-293.

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Addendum: Since preparing this report, we have learned that the mother of our acardius has recently delivered, at another institution, a chromosomally normal, male singleton with multiple congential anomalies.