

Coarctation of the aorta, interrupted aortic arch, and hypoplastic left heart syndrome in three generations

Salvatore Gerboni, Giuseppe Sabatino, Rita Mingarelli, Bruno Dallapiccola

Abstract

Five members in three generations of a family were affected by a congenital heart disease. Four of them had mild or severe coarctation of the aorta (CoA), either isolated or in association with other cardiac defects. Fetal echocardiography allowed prenatal diagnosis in one pregnancy at risk. This family suggests that a rare form of CoA could be the result of an autosomal dominant mutation with high penetrance and variable expressivity rather than polygenic inheritance

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Most cases of coarctation of the aorta (CoA) are attributed to multifactorial inheritance. However, sporadic families presenting with CoA in two or more generations have suggested that sometimes this malformation could be inherited as an autosomal dominant trait with high penetrance and variable expressivity.¹

We report on a family in which CoA was segregating through at least three generations and in which fetal echocardiography allowed prenatal diagnosis in a pregnancy at risk.

Case reports

The proband, a 25 year old pregnant woman, requested echocardiographic monitoring of her second pregnancy. She was the third born of a sibship of three (III·3) (fig 1). She was born at term after an uncomplicated pregnancy. A diagnosis of CoA with interventricular septal defect (VSD) and patent ductus arteriosus (PDA) had been made at 20 months. The defect was corrected at 8 years. At that time chromosome analysis showed a 46,XX karyotype. One younger sister (III·1) died at 6 years of unspecified congenital heart disease (CHD). According to hospital records she had no features of any syndrome associated with cardiac outflow tract defect, such as Di George syndrome (DGS) and velocardiofacial syndrome (VCS). One younger brother (III·2) was healthy with normal cardiac function and structure, as shown by echocardiography.

At 22 years this woman became pregnant. In the 33rd week of gestation she delivered a male infant with a birthweight of 2300 g. The baby (IV·1) had interruption of the aortic arch and died at 6 days of age. An echocardiographic examination was performed in her second pregnancy at 26 weeks. A single fetus was found in cephalic position with a normal heart position and situs. A transverse thoracic sec-

tion of four chambers showed enlarged right atrium and ventricular cavities, and hypoplastic left atrial and ventricular cavities, with concordant and perforate atrioventricular valves. The foramen ovale was patent and not restrictive. The longitudinal view of the left heart showed normal mitral-aortic continuity with a perforate aortic valve and a hypoplastic ascending aorta. A transverse section of the great arteries showed normally related vessels with a hypoplastic aortic root and dilated pulmonary trunk. There was a patent ductus arteriosus without periductal turbulence on colour flow mapping. Chromosome analysis of amniocytes showed a 46,XX karyotype. A female infant was delivered at 39 weeks of gestation, with a birthweight of 2620 g (IV·2). Neonatal echocardiography confirmed the diagnosis of hypoplastic left heart syndrome and also showed severe narrowing of the aortic isthmus. The baby died at 10 days, soon after the Norwood procedure. She had no thymic hypoplasia, no deficit of cellular immunity, and no clinical features of DGS. The maternal family history was then re-evaluated. The father was the second born in a sibship of five. All the paternal brothers and one sister were healthy. Echocardiography of the father was unremarkable. The mother (II·1) was the second born in a sibship of three. The first sister and one brother were apparently healthy, but they were not available for cardiological evaluation. Their nine children were also healthy. The mother of the proband was examined by echocardiography, which showed a significant kinking of the aortic arch, without obstruction or gradient.

Discussion

In this family, five members in three generations had congenital heart disease. In four of them CoA of differing severity was documented, ranging from kinking of the aortic isthmus to interrupted aortic arch, either isolated or associated with other cardiac defects. Associated defects included interventricular septal defect, patent ductus arteriosus, and hypoplastic left heart. An autosomal dominant pattern of inheritance with high penetrance and variable expressivity was apparent in this pedigree.

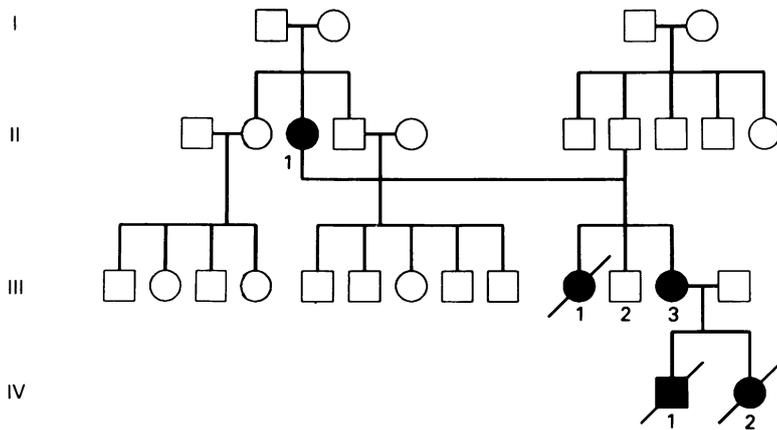
As in most cases of CHD, isolated CoA is also considered to show polygenic inheritance. The recurrence risk of some form of cardiovascular disease in sibs of probands with CoA was estimated to be less than 1 in 200 by Campbell and Polani,² 1% by Boon and Roberts,³ and

Servizio di Patologia Neonatale and Cattedra di Puericultura, Università di Chieti, 66100 Chieti, Italy.
S Gerboni
G Sabatino

Cattedra di Genetica Umana, Università di Tor Vergata, Roma, Via Ramazzini 15, 00151 Roma, Italy, and CSS Hospital, San Giovanni Rotondo, Italy.
R Mingarelli
B Dallapiccola

Correspondence to Dr Dallapiccola.

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Family pedigree.

1.8% by Zetterquist⁴ and Nora *et al.*⁵ According to Beekman and Robinow,¹ CoA did not affect more than two generations in 25 of 26 families reviewed. In one family, five members in four generations were affected, suggesting the segregation of an autosomal dominant trait with high penetrance and variable expressivity. An additional familial case of CoA associated with aplasia cutis congenita in the midline of the scalp vertex has been reported by one of us (BD).⁶ The possibility that these defects were the result of a Mendelian mutation has been put forward.

Interestingly, a study of relatives of infants with hypoplastic left heart syndrome (HLHS), which was present in one of our family members, has shown that cardiac defects occur in first degree relatives of probands at a higher frequency than predicted by an additive multifactorial model of inheritance. It was also found that first degree relatives of HLHS

probands may have an increased risk of sub-clinical cardiac defects.⁷

The present observation, together with a limited number of known families, supports the conclusion that a rare form of CoA could be the result of an autosomal mutation. This possibility should be taken into account when providing genetic counselling. Recent observations have shown that 22q11 deletions are associated with both DGS and VCS.^{8,9} This deletion can cause apparently isolated heart defects whose range may be wider than previously recognised in the two syndromes. Admittedly no patient in our family had the clinical features of DGS or VCF. However, the possibility that patients with a cardiac outflow tract defect, including isolated ventricular septal defects or coarctations, have an undetected deletion of 22q11 cannot be excluded.

- 1 Beekman RH, Robinow M. Coarctation of the aorta inherited as an autosomal dominant trait. *Am J Cardiol* 1985;56:818-9.
- 2 Campbell M, Polani PE. The aetiology of coarctation of the aorta. *Lancet* 1961;i:463-8.
- 3 Boon AR, Roberts DF. A family study of coarctation of the aorta. *J Med Genet* 1976;13:420-3.
- 4 Zetterquist P. *A clinical and genetic study of congenital heart defects*. Thesis, Institute of Medical Genetics, University of Uppsala, Sweden, 1972.
- 5 Nora JJ, Berg K, Nora AH. *Cardiovascular diseases. Genetics, epidemiology and prevention*. New York: Oxford University Press, 1991.
- 6 Dallapiccola B, Giannotti A, Marino B, Digilio C, Obregon G. Familial aplasia cutis congenita and coarctation of the aorta. *Am J Med Genet* 1992;43:762-3.
- 7 Brenner JJ, Berg KA, Schneider DS, Clark EB, Boughman JA. Cardiac malformations in relatives of infants with hypoplastic left-heart syndrome. *Am J Dis Child* 1989;143:1492-4.
- 8 Wilson DI, Cross IE, Goodship JA, *et al.* DiGeorge syndrome with isolated aortic coarctation and isolated ventricular septal defect in three sibs with a 22q11 deletion of maternal origin. *Br Heart J* 1991;66:308-12.
- 9 Scambler PJ, Kelly D, Lindsay E, *et al.* Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet* 1992;339:1138-9.