Congenital heart defects—the risks to offspring

Individuals with major heart defects are now surviving to adulthood in increasing numbers. Assumptions that risks of recurrence in offspring would prove to be similar to those for siblings have been called into question by two recent reports.^{1,2} In a largely prospective study, Whittemore *et al.*¹ identified 372 offspring of women with heart defects and found that 60 (16.1%) had a cardiac anomaly, and Emanuel *et al.*² reviewing patients with atrioventricular septal defects found that five of their 52 offspring had a major cardiac defect.

Heart defects in general

Whittemore *et al.*¹ found a much higher incidence of heart defects in offspring than was found in earlier studies, and also higher than that found by Czeizel,³ whose retrospective examination of 246 children born to patients who had had cardiac surgery for congenital defects showed a recurrence risk of 4.9%. Enrolment in Whittemore's study was voluntary and no record of refusals was possible, which raises the possibility of ascertainment bias. Although 48 women had had children previously, only one of these had a defect (a persistent ductus), so bias through volunteers having a special risk is less likely but cannot be totally excluded. Exclusion of two cases with dominant genetic syndromes, four with a positive family history, and three with a history of possible teratogenic exposure reduced the recurrence rate to 13.5%. Ventricular septal defects closed spontaneously in 14 children; 12 before the age of 3 years. Though such defects do constitute pathological conditions and should be considered in genetic analysis, in terms of practical advice they could be excluded, giving an overall risk of 7.9%.

By including only those girls in need of follow up throughout adolescence, Whittemore focused attention on the most severe defects. Those with continuing poor heart function or persistent cyanosis had more frequent miscarriages, but their offspring did not seem more prone to structural malformations than the children of women with good cardiac function. Since only women were considered, it may be suggested that female probands face a higher risk than males. It is, however, more likely that the unusually frequent recurrence in Whittemore's study is the result of having selected a study population with a different genetic predisposition.

Multifactorial model

When considering genetic models, specific types of defect should be considered separately rather than looking at pooled data: the multifactorial model agrees well, for example, with the findings of persistent ductus arteriosus. There is good evidence for a polygenic predisposition. Zetterqvist⁴ examined the siblings and offspring of 435 affected individuals. After excluding two families with evidence of a single dominant gene defect the recurrence risk was 2.3% for siblings and 2.5% for offspring. As predicted in a polygenic trait, these approximate to 2.4% which is the square root of the population incidence. The genetic factors probably relate to histological abnormality of the duct wall, and possibly variation in the speed of maturation in the third trimester.

Dennis and Warren⁵ examined 308 offspring of patients with ventricular septal defects, right ventricular outflow obstruction, or combinations of these and found 9 (3.4%) with a heart defect. This resembles the risk for siblings and is therefore in agreement with the multifactorial model, but does not in itself prove the model. Heterogeneity within the diagnostic categories could mean that single gene defects were accounting for some cases, but these could not be distinguished. In particular, new mutation autosomal dominant gene defects could cause major heart anomalies too severe to permit reproduction, so preventing their recognition.

In the Whittemore report, 8 of 27 children born to mothers with valvar aortic stenosis had a heart defect. Although this implies a contribution by single dominant genes, it can be seen that even in this large study subdivision according to type of defect results in small data sets.

Atrioventricular septal defects

These vary from the isolated ostium primum atrial septal defect to those with atrial and ventricular communication and a common valve orifice. The deficiency of the atrioventricular septum itself does not vary, however, only the attachment of the valve apparatus to its margins, so the different varieties may be analysed as a single pathological entity.

Even before the latest study,² the multifactorial model seemed inappropriate in this group. Trisomy 21 accounts for approximately one third of cases and this strong association suggests that a gene or genes

on chromosome 21 may have an important influence on endocardial cushion growth or adhesion. In 1968 Yao *et al.*⁶ reported four siblings suffering from isolated ostium primum atrial septal defect with normal parents. O'Nuallain⁷ reported a large pedigree in which this trait behaved as an autosomal dominant. Nora⁸ found no recurrence in siblings in 70 families, then found 4 siblings with an atrio-ventricular septal defect in one family. Sanchez-Cascos⁹ found recurrence in 14 of 161 first degree relatives (8.7%). The 10% recurrence risk noted by Emanuel *et al.*² adds further weight to the proposition that in some non-syndromic cases this defect results from a single gene defect, while environmental insults are of little consequence.

Conclusion

It is still reasonable to give most patients with congenital heart defects a 5% recurrence risk for an important cardiovascular malformation in offspring, and to interpret this as a relatively small risk. In cases of aortic or pulmonary valve stenosis and atrio-ventricular septal defect, an empirical risk of 5–10% seems more appropriate, and where prenatal diagnosis using fetal echocardiography is available, it is reasonable to offer this facility. These reports illustrate the value of examination of offspring in studies of aetiology and suggest that genetic factors may be more important than realised.

References

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