Evidence of congenital heart disease in the offspring of parents with atrioventricular defects

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SUMMARY Fifty-two of the 56 offspring from 90 patients with proven atrioventricular defects were examined. There were five with congenital heart disease. The defects were concordant in three and discordant in two. The mother was the affected propositus in all cases. In this relatively small sample the incidence of congenital heart disease in the offspring of parents with atrioventricular defects was 9.6%, or 14.3% if only the female propositi were considered. This is a much higher figure than that reported for the simple forms of isolated congenital heart disease.

The term atrioventricular defect, introduced by Bedford *et al.*,¹ has been used to include patients with ostium primum defect, common atrioventricular canal, and single atrium, as previously described.²

In our original study of atrioventricular defects³ we accepted 92 propositi in an attempt to determine the frequency of congenital heart disease in their first degree relatives. We reported that two of the 184 parents were affected, giving a frequency of 1.1%, four of the 229 sibs, a frequency of 1.7%, and two of the 20 children, giving a frequency of 10.0% which seemed surprisingly high. Subsequent studies of other forms of congenital heart disease have shown similar findings for parents and sibs.⁴

Recently we reviewed these data for errors as the diagnosis in 1968 in 20 of the propositi had been accepted on clinical and electrocardiographic evidence alone without confirmation from haemodynamic studies, surgery, or necropsy. In seven of the 20 the diagnosis was subsequently confirmed either by necropsy (four), or surgery (three), but in the remaining 13 the diagnosis was either unconfirmed (nine), or wrong (four). In three of the four errors there was a secundum atrial septal defect with left axis deviation, and the other propositus had a ventricular septal defect.

If these 13 families were omitted from the original study, slightly different figures resulted. Only one of the 158 parents had congenital heart disease, a frequency of 0.63%, and three of the 216 sibs, a fre-

quency of 1.4%. In both families in which there was thought to be an affected child, the propositus had been incorrectly diagnosed, and was subsequently shown to have a secundum atrial septal defect and left axis deviation,⁵ rather than an atrioventricular defect. Thus, none of the original 20 children was affected.

The present study was undertaken to expand these data and determine the frequency of congenital heart disease in children, one of whose parents had an atrioventricular defect. In addition to the 13 families already discussed, we discarded a further 19 from the original 92 because 14 of the propositi had died before the age of 16 years (none had borne children), and five could not be traced. Thus, 60 of the original 92 families were available, and a further 30 were added, giving a total of 90 families.

Subjects and method

All the propositi were over the age of 16 years. In 83 there was an ostium primum defect with varying degrees of cleft atrioventricular valves (11 of these also had a secundum atrial septal defect). In six there was a single atrium, and one had a common atrioventricular canal. The diagnosis was confirmed at operation (80), after clinical examination and haemodynamic studies (six), or at necropsy (four). There were 32 male and 58 female propositi. They produced 56 children, 52 of whom were available for examination. In 36 the mother was the affected parent, and in 16 the father. None of the propositi or offspring had Down's syndrome.

The method of data collection, which involved

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interviewing the *propositi* and examining the offspring, was arranged as in previous studies.^{3 5 6} All children had a clinical examination, an electrocardiogram, a chest radiograph, and, where possible, an echocardiogram.

Results

Fifty-two (92.8%) of the 56 children were examined: four (7.7%) had congenital heart disease. In all four cases the mother was the affected parent. The atrioventricular defects in the mothers had been repaired at the ages of 15, 16, 17, and 19 years, respectively. The average age of these *propositi* at the time of birth of the affected child was 25.7 years. This did not differ significantly from the average age of the *propositi* at the time of birth of the 48 normal children, which was 26.0 years for the female *propositi* and 28.1 for the male *propositi*.

Details of the four affected children are given in the Table. Two had Fallot's tetralogy: one, the first born of two, birthweight 1.79 kg, had successful corrective surgery at the age of 2 years 2 months; the other was the second of two children, birthweight 3.32 kg, and died at operation aged 8 months. The remaining two affected children had atrioventricular defects. One was the first born of three, birthweight 3.34 kg. The defect was successfully closed and mitral valve repaired at the age of 3 years 6 months. The other was the first born of two who had a birthweight of 3.42 kg and died after operation at the age of 11 months. This child, in addition to an atrioventricular defect, had a stenotic double mitral orifice.

A further child was thought to be affected; again the mother was the *propositus* having both *primum* and *secundum* atrial septal defects. The mitral valve

was abnormal, thickened but not cleft. The defects were repaired at the age of 19 years and she gave birth to a child three years later. The child was examined at the ages of 13 and 25 months and was found to have a partial right bundle-branch block, and left axis deviation of -62° and -45° , respectively. There was also an ejection systolic murmur, some movement of the second heart sound with respiration, and the chest radiographs suggested pulmonary plethora. No other investigation was done and the child has been lost to follow-up. The diagnosis therefore rests between an atrioventricular defect and a *secundum* defect with left axis deviation. If accepted as an affected offspring, then five of the 52 children would be affected, giving a frequency of 9.6%.

Maternal smoking and drinking habits in the 19 female *propositi* during 35 pregnancies, including one twin pregnancy, were unremarkable. None was a heavy smoker though four women smoked between 20 and 25 cigarettes a day during eight pregnancies. Two women consumed regular alcohol during four pregnancies. In one of these, consumption was excessive (six gins and two glasses of wine per day), and this *propositus* was one of the two heaviest smokers (25 cigarettes per day).

In the five pregnancies which produced the affected children (including the child with a right bundle-branch block and left axis deviation), three of the mothers were non-smokers, and two smoked more than 20 cigarettes a day. One of the mothers who was a non-smoker did not consume alcohol. The remaining four admitted to an occasional drink. Thus, there was nothing in the maternal drinking and smoking habits which suggested that these teratogens played a significant role, but the sample of 19 women and 36 pregnancies was small. None of the mothers was hav-

Table Clinical data on *propositi* and their five affected children

<i>Propositus</i>				<i>Affected offspring</i>					
<i>Family</i>	<i>Sex</i>	<i>Age (y)*</i>	<i>Congenital heart defect</i>	<i>Birth order</i>	<i>Birthweight (kg) and sex</i>		<i>Age and outcome at operation</i>		<i>Operative findings</i>
1	F	19	Single atrium, AV canal, cleft mitral valve, abnormal tricuspid valve, pulmonary valve stenosis	1	1.79	F	2 y 2 mth	Alive	Fallot's tetralogy
2	F	32	Ostium <i>primum</i> , cleft mitral and tricuspid valves	2	3.32	M	8 mth	Dead	Fallot's tetralogy
3	F	22	Ostium <i>primum</i> , cleft mitral valve	1	3.34	F	3 y 6 mth	Alive	Ostium <i>primum</i> , cleft mitral valve, abnormal tricuspid valve
4	F	30	Ostium <i>primum</i> , cleft mitral valve	1	3.42	M	11 mth	Dead	Intermediate type AV canal, double mitral orifice
5	F	22	Ostium <i>primum</i> and <i>secundum</i> atrial septal defect, abnormal mitral valve	1	3.58	M	No operation ?		

*Age of mother at birth of affected child.

ing any medication during their five pregnancies and there was no consanguinity in their families.

Discussion

In the five affected children, three had concordant, and two discordant lesions, and in all cases it was the mother who was the affected parent. The sample is too small to draw conclusions, particularly as atrioventricular defects when non-familial occur twice as commonly in females as in males.

Nora and Nora's⁴ studies of affected offspring of parents with simple congenital heart disease such as ventricular septal defects, persistent ductus arteriosus, secundum atrial septal defects, Fallot's tetralogy, pulmonary stenosis, coarctation of the aorta, and aortic stenosis showed that the risk of producing an affected offspring varied from 2 to 4%. It appears from our study that the risk of producing an affected child when one parent has an atrioventricular defect is higher, between 7.7 and 9.6%. If only the 19 female propositi are considered, then the number of affected children is even higher, being five out of 35 pregnancies—14.3%. We accept that our total sample is small, namely 52 offspring, and this may have provided a falsely high number of affected children.

In a similar study of 160 propositi with Fallot's tetralogy, however, which was run in parallel with the study on atrioventricular defects, 45 of the propositi produced 79 offspring. Seventy-eight were examined and three (3.8%) had congenital heart disease which agrees with Nora and Nora's findings.⁴

The frequency of atrioventricular defects in the normal population is less than 1%.⁷⁻¹⁰ In many chromosomal abnormalities, especially the trisomies, the incidence of congenital heart disease is considerably higher.¹¹ In Down's syndrome this particularly applies to atrioventricular canals, but it probably does not imply a simple gene dosage effect. These comments, however, are not relevant to the present study as Down's syndrome was not present in any of the propositi.

Unfortunately our numbers are too small to make more than speculative comments on the genetic and environmental influence on the aetiology of atrioventricular defects. There appeared to be a strong maternal influence which from preliminary studies was unrelated to smoking and alcohol consumption. The mode of inheritance appeared to be complex, for simple Mendelian inheritance was not seen. If genetic and environmental factors combine to give an underlying predisposition with a threshold above which congenital heart disease was seen, then the increased incidence among females suggested that the average liability in females was greater than in males. If relevant to atrioventricular defects it would imply that all first-

degree relatives should exhibit the same incidence of the disease. Our data, however, did not conform with this, for we have found that the incidence among the children of the propositi was greater than that among the sibs. In addition, one would expect more children of the male propositi to be affected than the children of the female propositi, and this was not the case in our sample. Thus, the fact that all affected offspring were from female propositi remains unexplained and may again be the result of the small sample studied.

Our data do not allow us to postulate a definite mode of inheritance for atrioventricular defects. It certainly does not follow a simple pattern but, like other forms of isolated congenital heart disease, both genetic and environmental factors are probably involved.

From this study we conclude there is an increased incidence of affected offspring in mothers with atrioventricular defects. This appears to be higher than in the offspring of parents with more simple forms of congenital heart disease. The lesions in the offspring may be concordant or discordant. It should be emphasised to prospective mothers with an atrioventricular defect, who seek counselling before or during pregnancy, that their child is more likely to be normal than abnormal but, if they do have an affected child, the defect is likely to be amenable to operation, but whether this is successful depends on many factors. Two of our affected children died at operation, which was related to their age and difficult anatomy. In view of the high incidence of affected offspring in these mothers, we suggest that echocardiographic assessment of the fetal heart should be part of their routine antenatal supervision. Normal findings would do much to reassure mothers who, understandably, have special anxieties as they have suffered the problems of congenital heart disease.

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