Recurrence Risks in Children Having One Parent with a Congenital Heart Disease

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SUMMARY The risk of recurrence of a congenital cardiovascular malformation in a child having one parent with congenital heart disease has been determined for each of the seven most common anomalies presently compatible with survival to reproductive age. The range of risk is 2.5% to 4.3% depending on the lesion. This is within the range of expectation for the model of multifactorial inheritance previously used to predict recurrence in other first-degree relatives of probands (siblings and parents) with congenital heart disease. The cardiovascular abnormality occurring in the child was most often the same as in the parent or was a closely related variant of it.

This report brings together previously published segments and makes available our completed data on recurrence risks to offspring of parents with seven common and significant congenital heart lesions compatible with survival to a reproductive age. The theoretical and empirical bases of these studies have been developed over the past decade and will only be briefly reviewed here.

Patients and Methods

These data have been obtained over the past 15 years in Madison, Montreal, Houston and Denver. Our goal was to evaluate personally at least 100 children of affected parents for each of the seven cardiovascular defects under investigation. The personal evaluation included the documenting of the cardiovascular lesion in the parent and offspring by diagnostic methods appropriate for each case. With two exceptions this goal has been achieved. The exceptions are tetralogy of Fallot and coarctation of the aorta. In these categories we have added: to our 42 offspring of parents with tetralogy, the published cases of Taussig et al. and unpublished material of McNamara; and to our 62 offspring of patients with coarctation of the aorta, the published cases of Zetterqvist.

Care has been taken to eliminate from the data base families which have Mendelian (single gene) syndromes or chromosomal disorders. These cases would, of course, introduce a bias, mainly reflecting the recurrence risks of single mutant genes. The recurrence of heritable chromosomal disorders with congenital heart diseases is negligible. The current distribution of categories of cases being seen in our clinic is given in table 1.

Results

Table 2 summarizes our recurrence data and reveals a risk that is relatively small and within the range of expectation for recurrence in first-degree relatives as predicted by the square root of the population frequency (s^2), one of the simpler models of multifactorial inheritance. We have discussed this approach elsewhere and it was not our purpose in this study to test the multifactorial hypothesis. The risk as given is for the first recurrence of a congenital heart lesion if there is only one affected parent. The risk is for any congenital heart lesion, but the majority of these patients had either the same lesion as the parent or a variant of it (e.g., a parent with an atrial septal defect [ASD] having a child with ASD and pulmonary stenosis).

If both parents have congenital cardiovascular malformations or if there is an affected parent and one affected child, the risk would be at least tripled, as has been found in our empirical data for recurrence of congenital heart anomalies in the presence of two affected first-degree relatives. To date we have only one example of a child born to two parents with congenital heart diseases (one parent had ventricular septal defect, the other had aortic stenosis). The child was normal. Our concern would be greater if both parents had the same heart defect.

Discussion

The children who would have died in earlier decades have, through the medical and surgical advances of the past 25 years, grown to maturity and wish to know what the risks are that their children will have congenital cardiovascular diseases. The seven most common congenital cardiovascular anomalies presently compatible with survival to adult age have been studied to answer this question. Answers may also be found for other anomalies such as transposition of the great arteries and tricuspid atresia as enough of these patients are managed over the next decades to the age of reproduction.

The recurrence risk is in the range of 2–4% and follows the pattern for recurrence in siblings, that the more common the congenital heart lesion the higher is the frequency of recurrence. However, if one mixes families with multifactorial inheritance and families with Mendelian inheritance to arrive at recurrence risks, meaningless figures result. It is hoped that the infrequent patient with a Mendelian disorder is recognized by the syndrome of which the heart lesion is a part, and that the 1 in 2 or 1 in 4 risk is appropriately applied. As a general rule, heart defects produced by single mutant genes are part of a syndrome. The rare exceptions, such as idiopathic hypertrophic subaortic stenosis are autosomal dominant. We are not familiar with recessively inherited cardiovascular anomalies which are not part of a syndrome. The risk figures that are needed for the majority
of families are those for multifactorial inheritance, which are provided here in table 2.

These cautions must be emphasized for those who are going to undertake the counseling of families with congenital heart diseases. It is essential to know what the specific congenital heart lesion is, and what the family pedigree shows. For example, a parent with pulmonary stenosis who does not have a Mendelian syndrome, who has a spouse with no congenital heart disease and no other children with congenital heart disease, should be counseled that the risk to a subsequent child is 3%. If the mother has Ulrich-Noonan syndrome, half of her children will have this dominantly inherited syndrome and half of those with the syndrome will have heart disease—a 25% recurrence risk rather than a 3% recurrence risk.

As another example (fig. 1), a mother with atrial septal defect whose mother and only sibling also have atrial septal defect wants to know what the chances are that she will have a child with congenital heart disease. Her husband is free of cardiovascular disease and she has no clear-cut limb anomaly of the Holt-Oram type. This family should be considered a high risk family until proved otherwise. Perhaps careful inspection of other family members would reveal a minor limb anomaly which would support dominant inheritance. Whether the pedigree would be interpreted as type C (high risk multifactorial) or autosomal dominant, an initial recurrence risk of 50%, not 3%, would be given by us.

The implications to society continue to be of concern. Will the medical and surgical interventions which preserve to reproductive age the children who would have died of congenital heart disease, increase the genetic load and social burden we all must bear? Our data are still insufficient to answer this question, but a trend we noted in an earlier publication, that individuals with congenital heart disease are marrying less frequently, marrying later and having fewer children than the general population continues throughout this series. There appears to be voluntary abridgement of reproduction. Whether this will favorably affect the genetic load or social burden remains to be evaluated over the next generations.

References

Table 1. Etiologic Basis of Congenital Heart Disease

<table>
<thead>
<tr>
<th>Primarily genetic factors</th>
<th>Primarily environmental factors</th>
<th>Genetic-environmental interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal</td>
<td>Rubella</td>
<td>(multifactorial inheritance)</td>
</tr>
<tr>
<td>Single mutant gene</td>
<td>Other</td>
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</table>

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Number</th>
<th>%</th>
<th>Exp √p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarctation of aorta*</td>
<td>7/253</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>5/199</td>
<td>2.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>7/174</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Tetralogy of Fallot†</td>
<td>6/141</td>
<td>4.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>6/139</td>
<td>4.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>4/111</td>
<td>3.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>4/103</td>
<td>3.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>39/1120</td>
<td>(3.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes cases of Zetterqvist.†
†Includes cases of Taussig and McNamara (unpublished observations).
‡Exp √p = expectation for occurrence in a first-degree relative as predicted by the square root of the population frequency.

Figure 1. This family with atrial septal defect has such a high concentration of affected first-degree relatives that prudent counseling would recognize it as high risk even in the absence of stigmata of Holt-Oram syndrome. Whether it represents autosomal dominant or type C multifactorial inheritance is speculative.
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