Familial Atrial Septal Defect with Prolonged Atrioventricular Conduction

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SUMMARY This report describes a family with frequent recurrence of congenital heart disease in multiple generations. Eight members had atrial septal defect (ASD) of the fossa ovalis type and seven members had other forms of congenital heart disease. One branch of the pedigree showed a predominance of ASD with prolonged atrioventricular (A-V) conduction and initially suggested an autosomal dominant gene effect. A variety of other forms of congenital heart disease were found in several first degree relatives of those with ASD as well as in more distant relatives. The variability of congenital heart disease in this pedigree is compatible with the polygenic mode of inheritance. Definition of the inheritability of congenital heart disease in a specific family has important consequences in the determination of the recurrence risks for all family members.

SECUNDUM ATRIAL SEPTAL DEFECT (ASD) is known to recur in some families suggesting a hereditary predisposition.1-15 Recent twin studies and large population surveys of families with one or more affected members indicate that ASD usually does not conform to a simple dominant or recessive mode of inheritance but follows a multifactorial or polygenic pattern.16-18 Thus, first degree relatives of an affected individual have a 35-40 times greater risk for ASD than the general population, about 3% compared to 0.08%.17, 20, 21 Moreover, recurrence risks increase with each additional first degree relative affected. Genetic counselling may be complicated by the clustering of numerous affected family members in successive generations simulating a single dominant gene effect.8-13

Several previous reports suggest that the presence of prolonged atrioventricular (A-V) conduction with secundum ASD might be a useful clinical marker indicating a dominant mode of inheritance.1, 11-14 If this were correct, then offspring of an affected individual could have a 50% or 1:2 chance to have the same congenital heart disease, or some modified form thereof, quite independent of other affected members. We recently studied a similar family with clustering of at least four successive generations affected with ASD and prolonged A-V conduction. In addition, several other family members were found to have a variety of different congenital heart defects. Providing accurate genetic counselling for members of such a family represents a complex task not only for the cardiologist with limited exposure to such problems but also for the genetic counselor. In this report, we review our attempts to estimate recurrence risks for various members of this family with a high frequency of

*Risk estimates of polygenic traits are empirical values based upon the observed recurrence of the trait after a proband has been identified.15, 20, 21 These risks for first degree relatives approximate the square root of the prevalence of the particular cardiac anomaly and thus represent only marginal probabilities. With each additional affected first degree relative, recurrence risks increase as theoretically estimated by Smith.22 In general, recurrence risks decrease as a function of the degree of relatedness to the affected individual.24

Clinical Analysis

Eighty-nine members of the family were ascertained via IV.13 (fig. 1). Fourteen were unavailable for examination. Office records and historical information were available for three members. Seventy-two relatives were evaluated by detailed history, physical examination, and electrocardiographic recordings.

ASD was found in eight members (table 1). The diagnosis was confirmed by cardiac catheterization and surgery in seven patients and by catheterization alone in one. Six had fossa ovalis type defects (IV.10, IV.11, IV.13, V.19, V.20, V.24) and one (V.26) had a large ASD with an additional ventricular septal defect. The eighth patient, III.4, developed symptomatic complete heart block during a right heart catheterization at age 55. The catheter apparently passed from the right atrium to a pulmonary vein presumably through an atrial septal defect. Because of the heart block, the study was not completed and oxygen samples were not obtained. A permanent pacemaker was eventually inserted and the patient refused further study. Physical examination revealed a Grade IV ejection systolic murmur at the second left sternal border with fixed splitting of the second heart sound. Chest X-ray revealed enlarged pulmonary arteries and increased vascular markings.

Other family members are known to have had "heart trouble." Office records from the personal physician of member III.1 described a systolic murmur and an enlarged liver at age 31. Chest X-ray showed an enlarged heart and prominent hilar area. This patient was continuously disabled and suddenly died at age 48. His father, II.1, died at age 45 with a long history of "rheumatic heart disease," and the grandfather, I.1, died suddenly in his 40s. No further information was available on these patients.

During this study, member IV.11 died suddenly at age 38. A fossa ovalis defect had been closed surgically at age 31 and he had remained completely asymptomatic postoperatively. A systolic ejection murmur, Grade I/VI, persisted along the left sternal border and first degree heart block was consistently noted by electrocardiograms. The evening before his sudden death he complained of a
headache and a feeling of indigestion. Preliminary autopsy examination, performed by Dr. Maurice Lev's laboratory in Chicago, revealed normal coronary arteries, marked fenestration of the aortic valve, and muscular subaortic stenosis of the left ventricle. A conduction system analysis of this heart is being completed.

Seven members have other forms of CHD. Diagnosis was determined by cardiac catheterization and surgery in three members to be coarctation of the aorta (V.14), tetralogy of Fallot and patent foramen ovale (V.25), and ventricular septal defect (V.42). Two were diagnosed at autopsy to have tetralogy of Fallot with pulmonary atresia (V.27) and truncus arteriosus (VI.3). Two additional members were diagnosed on clinical grounds to have aortic stenosis (V.3) and ventricular septal defect (V.12).

Electrocardiographic Data

Prolonged A-V conduction was found in eleven patients, eight of whom had ASD, one had tetralogy, and two had no other abnormalities. Ten of the eleven were in sinus rhythm with first degree block (table 2). Member III.4, who was described above, progressed from a Mobitz II second degree block to complete heart block during the catheterization and then required a permanent pacemaker. Member V.19 developed intermittent Wenckebach second degree block eight years postoperatively. Her preoperative P-R interval at age seven was 0.20 seconds. The interval had progressed to 0.32 seconds when the intermittent second degree block appeared (fig. 2). His Bundle electrogram revealed prolongation of the A-H interval with a normal H-V time. Member V.20 had periodic sinus slowing with transient junctional escape rhythm and A-V dissociation which was not felt to be significant.

Additional Studies

Karotype analysis of 30 cells from each of the following members, V.19, V.24, and V.25, showed no evidence of chromosomal aberration by standard methods. None of the patients had finger-like hypoplastic triphalangeal thumbs or shoulder girdle anomalies characteristic of the Holt-Oram Syndrome or other malformations to suggest an associated syndrome. Several apparently normal individuals had soft systolic ejection murmurs with normal splitting of S2 that were considered to be insignificant, but further evaluation is planned.

Comments

The findings in this family underline the importance of thorough pedigree analysis and detailed diagnostic evaluation of family members as fundamental to any effort to deliver meaningful genetic counselling. Such analyses designate our family as having a particularly unfavorable
predisposition for recurrence of multiple forms of congenital heart disease. Nine of fifteen descendants of III.3 had congenital heart disease; seven had ASD, and two had some other form of CHD. Eight of the nine with congenital heart disease had first degree block and two others exhibited prolonged A-V conduction without disease. Unfortunately, the cardiac condition of III.3 is unknown. However, III.4 is known to have ASD and prolonged A-V conduction suggesting that II.1 may have transmitted the trait to both III.3 and III.4 and thus, III.3 may have passed it to all of his children. The succession of affected generations suggests a single dominant gene effect, but careful study of the pedigree may indicate otherwise. If a dominant gene were involved, each child of an affected parent would have a 1:2 chance or 50% risk; offspring of normal parents would have no risk unless this gene showed decreased penetrance, i.e., as suggested by members II.1 and III.3.

Descendants of III.3 in generation V exhibit other forms of congenital heart disease besides ASD. Indeed, despite the apparent absence of congenital heart disease in III.2 and III.5, their descendants are also affected with CHD other than ASD. Member III.4 had normal children and grandchildren, but a great grandson died of a severe form of congenital heart disease, truncus arteriosus. Clustering of ASD in the offspring of III.3 tends to obscure the occurrence of other congenital heart disease in other portions of the family lineage. Thus, this pedigree would appear to be more compatible with a polygenic mode of inheritance. Presumably, multiple genes affecting cardiac formation would have randomly segregated in "high density" in III.3 and his descendants while other lines reflect a more favorable distribution. The III.3 portion of the pedigree is an example of the high risk type C family as defined by Nora.8

The type of inheritance mode involved directly influences the type of counselling various members of the family may receive. In the polygenic mode of inheritance, all members of this family would have some risk for offspring with congenital heart disease. Experience with various forms of congenital heart disease indicates that a 30 to 40 times greater risk (3%) than the general population exists for each child after one is affected, and a two to three times greater risk (8 to 12%) after two first degree relatives are affected (see footnote above).

### Table 1. Members with ASD

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis (yr)</th>
<th>L-R Shunt</th>
<th>RVP (mm Hg)</th>
<th>Anatomic defect (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.4</td>
<td>55</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>IV.10</td>
<td>18</td>
<td>69</td>
<td>30/0</td>
<td>Secundum — 25 × 20</td>
</tr>
<tr>
<td>IV.11</td>
<td>31</td>
<td>40</td>
<td>40/7</td>
<td>Secundum — 25 × 30</td>
</tr>
<tr>
<td>IV.13</td>
<td>30</td>
<td>47</td>
<td>30/0</td>
<td>Secundum — Additional criboform openings 25 × 25</td>
</tr>
<tr>
<td>V.19</td>
<td>4</td>
<td>61</td>
<td>28/4</td>
<td>Secundum 20 × 20</td>
</tr>
<tr>
<td>V.20</td>
<td>6</td>
<td>66</td>
<td>28/5</td>
<td>Secundum 25 × 20</td>
</tr>
<tr>
<td>V.24</td>
<td>4</td>
<td>62</td>
<td>28/2</td>
<td>Secundum 15 × 15</td>
</tr>
<tr>
<td>V.26</td>
<td>4</td>
<td>77</td>
<td>90/9</td>
<td>Rim of atrial tissue and VSD</td>
</tr>
</tbody>
</table>

Abbreviations: L-R = left to right; PBF = pulmonary blood flow; RV = right ventricle; VSD = interventricular septal defect.

### Table 2. Members with A-V Conduction Disturbance

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis (yr)</th>
<th>P-R Interval (sec)</th>
<th>Rhythm</th>
<th>QRS in lead V1</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.4</td>
<td>55</td>
<td>0.30</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>IV.10</td>
<td>18</td>
<td>0.22</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>IV.11</td>
<td>31</td>
<td>0.22</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>IV.12</td>
<td>35</td>
<td>0.22</td>
<td>NSR</td>
<td>Normal†</td>
<td>ASD</td>
</tr>
<tr>
<td>IV.13</td>
<td>30</td>
<td>0.28</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>V.19</td>
<td>4</td>
<td>0.20</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>V.20</td>
<td>6</td>
<td>0.23</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>V.21</td>
<td>3</td>
<td>0.21</td>
<td>NSR</td>
<td>RAS Normal†</td>
<td>ASD</td>
</tr>
<tr>
<td>V.24</td>
<td>3</td>
<td>0.24</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD</td>
</tr>
<tr>
<td>V.25</td>
<td>3</td>
<td>0.20</td>
<td>NSR</td>
<td>Rs</td>
<td>Tetralogy</td>
</tr>
<tr>
<td>V.26</td>
<td>4</td>
<td>0.24</td>
<td>NSR</td>
<td>rSr'</td>
<td>ASD + VSD</td>
</tr>
</tbody>
</table>

Abbreviations: NSR = normal sinus rhythm.
†Diagnosis on clinical grounds.
‡Progressed to intermittent Mobitz I.

Smith has provided a model system for evaluating risks in multifactorial inheritance with variable numbers of affected parents and siblings.23 Based on the polygenic model and observed recurrence risks for congenital heart disease, offspring of IV.16, for instance, would have a 3 to 4% recurrence risk and those of IV.23 about a 0.5 to 1% risk. What then are the risks to descendants of III.3? Empirically, it would appear that the risk may be about, or higher than 50%. Using Smith's theoretical estimates for descendants of III.3, the risk may be almost equal to or even greater than that of a single dominant gene; offspring of IV.13 (one affected parent and four affected siblings) may be estimated to be at least 30 to 40% and may perhaps be greater. A significantly high risk would also exist for the offspring of V.22, V.23, V.28, and V.29 who are presumably normal. Risks to offspring of the other descendants of the III generation would decrease significantly with each normal relative separating them from an affected individual, but all members would have a risk greater than the population in general.

Kahler et al.11 first reported the association of prolonged A-V conduction and familial ASD. Bizarro et al.3 emphasized this combination as a sign of a single mutant autosomal dominant gene. They reported first degree block in 92% of their patients in sinus rhythm compared to the usual instance of 5 to 15% in sporadic ASD.26 They

![Figure 2. Upper strip] tracing from patient V.19, taken one year after ASD repair. Lower strip] eight years postoperatively demonstrating second degree (Mobitz I) heart block.
reviewed five previously reported families in the literature and found prolonged A-V conduction in 82% of the cases for whom adequate data was available.11 14

Our family is very similar to these but provides additional evidence reinforcing a multifactorial/polygenic mode of inheritance of congenital heart disease. In high risk families, one form of congenital heart disease may predominate, but usually, other types of congenital heart disease also occur. It is possible that in this family, ASD and the conduction aberration may result from a dominant gene effect and the other forms of congenital heart disease may be polygenic in origin. The distinction is important because, as indicated above, with a polygenic trait every member of the family has some risk for CHD, as opposed to the single gene trait in which only those offspring of an affected parent face significant recurrence risks.

Another aspect besides genetic counselling is the prognosis of the congenital abnormalities. Bjornstad15 reported a seventh family with familial ASD and prolonged A-V conduction and suggested that this type of ASD does not have a benign natural history. Four members of their family died early but none of these had had catheterization or autopsies performed to confirm the type of congenital heart disease that caused death. One of our patients, IV.2, died suddenly at age 38. However, autopsy findings revealed unsuspected congenital lesions of the aortic valve and muscular septum. Therefore, the possibility of associated congenital heart disease needs to be ruled out before the ASD or conduction system defect, per se, can be invoked as a cause of death. A final point is the nature of the conduction system defect itself. Involvement of the A-V node was confirmed in one of our patients by His bundle electrogram, and another member in our family and two in previously reported families11 showed complete nonsurgical heart block. Further conduction system analysis, as well as continued follow-up, is needed in all of these families.

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References

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