Familial Atrial Septal Defect with Prolonged Atrioventricular Conduction
A Syndrome Showing the Autosomal Dominant Pattern of Inheritance

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SUMMARY
Atrial septal defect (ASD) of the fossa ovalis type was found in 16 members of one family and confirmed in 15 members at autopsy or surgery or by cardiac catheterization. Sinus rhythm was present in 12 affected members, 11 of whom had electrocardiographic evidence of prolonged atrioventricular (A-V) conduction. Five other family members without ASD also had prolonged A-V conduction. The pedigree chart suggests that the syndrome ASD with prolonged A-V conduction is the manifestation of a single mutant autosomal gene with dominant effect, a high degree of penetrance, and some variation in expressivity. Earlier reports of familial ASD showing the autosomal-dominant pattern of inheritance reveal a similar frequency of prolonged A-V conduction among affected persons. The great majority of cases of ASD are sporadic, with little likelihood of recurrence in subsequent sibs or children. We suggest, however, that when ASD of the fossa ovalis type is accompanied by prolonged A-V conduction, the genetic prognosis may be drastically changed to a risk of almost 50% that the condition will recur in subsequent sibs or children of affected persons.

Additional Indexing Words:
Electrocardiography Atrial fibrillation catheterization Genetic counselling
Fossa ovalis

Most cases of congenital heart disease are sporadic; and even when the condition affects more than one member of a family, a simple mendelian pattern of inheritance is seldom seen. With regard to atrial septal defect (ASD), however, a small number of families has been reported in whom the pedigree charts suggest that the defect is transmitted according to the autosomal-dominant pattern of inheritance. The usual sporadic cases of ASD presumably are caused by the complex interplay of several genetic and environmental factors; and in those cases the risk that the defect will recur in subsequent sibs and children is very small—probably less than 2%. But when the defect is owing to a single mutant autosomal gene with dominant effect, the recurrence risk may approach 50%. Hitherto, in the absence of a typical previous family history, there has been no way of differentiating those cases with a bad genetic prognosis from the more usual variety; but recently we have investigated a family with many cases of ASD which afforded a clue that may help to separate the recurrent and the sporadic cases.

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Table 1

Type and Size of Proved ASD with Related Clinical Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis (yr)</th>
<th>Type of defect</th>
<th>Anatomic size (mm)</th>
<th>Measured L-R shunt (%)</th>
<th>RV pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.2</td>
<td>53</td>
<td>Fossa ovalis</td>
<td>17 by 17</td>
<td></td>
<td>55/10</td>
</tr>
<tr>
<td>I.3</td>
<td>43</td>
<td>(1) Fossa ovalis</td>
<td>25 by 25</td>
<td>43</td>
<td>30/3-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Between IVC and coronary sinus</td>
<td>10 by 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.4</td>
<td>54</td>
<td>Fossa ovalis</td>
<td>80 by 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.6</td>
<td>42</td>
<td>Fossa ovalis*</td>
<td>32 by 20</td>
<td></td>
<td>23/...</td>
</tr>
<tr>
<td>II.1</td>
<td>31</td>
<td>†</td>
<td></td>
<td>29</td>
<td>31/4...</td>
</tr>
<tr>
<td>II.9</td>
<td>29</td>
<td>Fossa ovalis</td>
<td>45 by 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.10</td>
<td>35</td>
<td>Fossa ovalis</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>II.11</td>
<td>21</td>
<td>†</td>
<td></td>
<td>43</td>
<td>30/4-11</td>
</tr>
<tr>
<td>II.13</td>
<td>16</td>
<td>†</td>
<td></td>
<td>61</td>
<td>13/7</td>
</tr>
<tr>
<td>III.1</td>
<td>9</td>
<td>Fossa ovalis</td>
<td></td>
<td>40</td>
<td>46/7</td>
</tr>
<tr>
<td>III.25</td>
<td>11</td>
<td>Fossa ovalis</td>
<td>15 by 15</td>
<td>62</td>
<td>44/0-4</td>
</tr>
<tr>
<td>III.29</td>
<td>5</td>
<td>Multifenestrated ostium secundum</td>
<td>18 by 12</td>
<td>42</td>
<td>30/4-2</td>
</tr>
<tr>
<td>III.31</td>
<td>1 mo</td>
<td>Fossa ovalis</td>
<td>10 by 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III.34</td>
<td>11</td>
<td>(1) Small defect adjacent to IVC</td>
<td></td>
<td>50</td>
<td>35/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Fossa ovalis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III.35</td>
<td>9 mo</td>
<td>Fossa ovalis</td>
<td>25 by 18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Rheumatic mitral stenosis as well as ASD.
†Defect proved by catheterization, not anatomically.

Report of Investigation of Family

The proband was a 42-year-old white woman (I.6) admitted for repair of an ASD of the ostium secundum type. On routine questioning, she informed us of five relatives with ASD. This led to a detailed investigation of her family.

Both parents of the proband were dead, and there is no reliable information about their cardiac status. We ascertained that there were five siblings, four children, 10 nephews and nieces, and 35 grand-nephews and nieces, making a total of 54 relatives to be investigated. Of these, five were dead—two older sibs, two nephews, and a grand-niece; autopsy data were available for the latter three. One niece (II.7) refused to allow any examination of herself or of her four children (III.21-24). This left 44 available relatives, all of whom were examined clinically and electrocardiographically. In those cases in which clinical findings were suggestive of ASD, cardiac catheterization was recommended; and this procedure was carried out in 10 cases. In addition, cytogenetic and dermatoglyphic investigations were made in some cases.

Findings

Clinical and Catheterization Data

Definite proof of the ASD was found in 15 family members (fig. 1): II.10 and III.31 at autopsy; I.2, I.3, I.4, I.6, II.9, III.1, III.25, III.29, III.34, and III.35 at surgery; II.1, II.11, II.13 by right-heart catheterization. (One additional member, II.8, has clear clinical evidence of a large interatrial shunt but defers further investigation or surgery.) In all cases diagnosed anatomically (table 1), the atrial sepal defect is of the fossa ovalis type (multiple defects in I.3 and III.34, a fenestrated defect in II.9). Family member III.35 had—in addition to an atrial sepal defect (25 by 18 mm)—a ventricular sepal defect (25 by 18 mm), pulmonary stenosis (infundibular, valvar with bicuspid valve, and post-valvular), moderate dextroposition of the aorta, and tricuspid stenosis. Member I.2 had rheumatic mitral stenosis as well as atrial sepal defect. Two other members of the family may have

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had congenital heart disease but no definite
diagnosis can be made: member I.1 died of
"heart trouble" at age 52 years and no records
of her cardiac status are available; and I.5,
who had been exempted from military service
because of a heart murmur, died suddenly at
age 42 years and no further information on his
heart condition is available.

Autopsy was performed on three members of
this family. Member II.2 died suddenly at age
25, while eating. The postmortem examination
revealed an intact interatrial septum and the
death was attributed to asphyxia secondary to
aspiration of food. Patient III.31 died of
bronchopneumonia at age 1 month, and a
large ASD of the fossa ovalis type was found.
Patient II.10 died of acute myocardial infarct-
ion, and autopsy confirmed the previous
findings of right-heart catheterization—an
ASD of the fossa ovalis type was found.

Family members II.5, III.11, and III.16
were suspected clinically of having ASD; and
diagnostic right-heart catheterization was rec-
ommended, but not accepted.

So of this family of 55 members, among the
48 on whom data could be obtained 15 have
been proved by autopsy, surgery, or cardiac
catheterization to have ASD, one has strong
clinical evidence of an ASD but has refused
further study, and three are suspected of
having the defect but either were too young
to justify right-heart catheterization or refused it.

Four of the five members who were found
to have an intact interatrial septum at the time
of right-heart catheterization had gradients of
7 to 10 mm Hg across the right-ventricular
outflow tract (table 2).

Electrocardiographic Data

Electrocardiograms were recorded from the
proband and all 44 of her available family
members except III.20, who was just 3 months
old. In addition, electrocardiograms were
available in the medical records of members
II.10 and II.31, who were dead. Altogether, 46
electrocardiograms were examined. Among
the 16 cases of ASD (table 3) there were four
with atrial fibrillation and 12 with sinus
rhythm. The latter 12 included 11 with P-R
intervals longer than the upper limits of
normal for age; in only one (II.11, age 21
years), the P-R interval was at the upper limit
of normal.

Among the five cases in which right-heart
catheterization excluded ASD (table 3), all
two of these in which it revealed a pressure
gradient between the right ventricle and the
pulmonary artery had prolongation of the P-R
interval. In the fifth case (III.33), in which
the hemodynamic findings were normal, the
P-R interval also was normal.

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**Figure 1**

Pedigree chart of family. Arrow indicates index case.

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Among the remaining 26 family members, in whom ASD was not suspected and cardiac catheterization was not performed, there were five with P-R intervals greater than the upper limits of normal. Thus, the 46 family members examined electrocardiographically included 20 with prolonged atrioventricular conduction, of whom 11 had ASD and another four were proved to have a pressure gradient between the right ventricle and the pulmonary artery.

**Laboratory Genetic Data**

There were no chromosomal anomalies in the five patients (I.6, II.1, III.1, III.34, and III.35) with atrial septal defect whose karyotypes were examined.
There were no abnormalities in the fingerprints and palm prints of the 24 patients studied thus.

**Pedigree Analysis (Fig. 1)**

The 16 family members with ASD included nine males and seven females. Inspection of the pedigree chart shows several examples of father-to-son transmission. X-linked inheritance therefore can be confidently excluded.

In the three generations studied, there are 25 individuals born to patients known to have ASD; and 11 (44%) of these 25 are also known to have ASD. This proportion is close to the 50% expected if the atrial septal defect was owing to a mutant autosomal gene with dominant effect and a high degree of penetrance. The several instances of parent-child transmission and, in the lineage of I.4, the transmission of ASD through three generations are also indications of the autosomal-dominant pattern of inheritance.

**Comment**

The familial occurrence of congenital heart disease is probably not uncommon. As methods of diagnosis have become more precise, an increasingly large number of families have been recognized in which several members present some form of congenital heart disease. A significant number of familial aggregates have been reported since 1932. The combined pedigree of Zetterqvist and Johansson and Stevens is the largest and has the highest number of involved subjects reported to date; 14 certain and five probable cases in four generations. We present a pedigree of 55 members, which includes 16 proved cases and three probable cases of ASD.

We have been particularly impressed by the high proportion of patients with ASD in this family who have prolonged atrioventricular conduction: 11 (92%) of the 12 with sinus rhythm. Reviewing the preoperative electrocardiograms of 100 consecutive cases of surgically confirmed ASD of the fossa ovalis type, we found 10 in which the P-R interval was above the upper limits of normal. This is similar to the findings in other series, in which prolonged P-R intervals were found in 5 to 15% of cases of ASD. (Some of these series may include instances of undetected familial involvement.) We have reviewed the electrocardiographic data reported by others from five families with ASD (table 4). In 14 (82%) of the 17 cases in which appropriate electrocardiographic data were available, the P-R intervals were prolonged. In the families reported by Weil and Allenstein and by Amarasingham and Fleming, all the patients with ASD had prolonged P-R intervals; and the same electrocardiographic anomaly was present in six of the eight patients reported by Kahler and associates. In the latter series, one of the patients had complete atrioventricular block; and so did one of our patients with atrial fibrillation.

The available information is limited, but it does seem that prolongation of atrioventricular conduction is very common among familial cases of ASD. This may be a valuable aid in

**Table 4**

**P-R Interval in Other Reported Families with ASD of Secundum Type**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reported cases</th>
<th>Adequate ECG data and NSR*</th>
<th>Prolonged P-R interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weil and Allenstein7</td>
<td>5</td>
<td>5</td>
<td>5†</td>
</tr>
<tr>
<td>Zuckerman and associates10</td>
<td>7</td>
<td>1</td>
<td>0‡</td>
</tr>
<tr>
<td>Kahler and associates15 (a)</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Kahler and associates15 (b)</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Amarasingham and Fleming16</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>17</td>
<td>14</td>
</tr>
</tbody>
</table>

*NSR = normal sinus rhythm.
†Three reported by authors; two measured by us from published electrocardiograms.
‡Measured by us from published electrocardiogram.
genetic counselling. If a patient presents with an ASD of the fossa ovalis type and prolongation of the P-R interval (and he is not taking digitalis), there is a strong possibility that his lesion is of the familial type and is the consequence of a single mutant autosomal gene with dominant effect. This is particularly true if there is an involved relative. Hence there is a substantially increased risk that subsequently born sibs of that patient will also have an ASD, and the risk of ASD among children of the patient approaches 50%—in striking contrast to the usual case of ASD with a recurrence risk of 2% or less. The situation may be analogous to that of cleft lip and palate: the great majority of cases are sporadic and the recurrence risk in the subsequent sibs and children of affected individuals is about 3%; but there are rare cases in which the cleft is accompanied by small pits in the vermillion part of the lower lip, and these cases are owing to a single mutant autosomal gene with dominant effect which makes the recurrence risk nearly 50%.17

In the family we are reporting, the ASD and the prolonged atrioventricular conduction are apparently two of the phenotypic expressions of the same mutant gene. A third expression may be mild obstruction to right-ventricular outflow. These multiple effects of the same gene are referred to as "pleiotropy." Some members of the family have all three expressions, but there are others with long P-R intervals only (II.5, III.2, III.16, etc.) and some with long P-R and right-ventricular outflow obstruction but no ASD (III.26, III.32, etc.). Thus the mutant gene in question, while being highly penetrant, shows variable expressivity—probably because of its interaction with other genes, or with exogenous influences, or with both.

Prolonged atrioventricular conduction is also common in the Holt-Oram syndrome.8,18 This syndrome also is produced by a single mutant autosomal gene with dominant effect. We suggest that physicians pay particular attention to the A-V conduction in all cases of ASD. If there is evidence of abnormal atrioventricular conduction, careful inquiry into the family history and, if possible, examination of close relatives should be undertaken. In this way sufficient evidence will be collected to test our hypothesis that ASD with prolonged atrioventricular conduction is often the effect of a single mutant gene and has a genetic prognosis which is substantially different from that of cases with normal atrioventricular conduction.

Acknowledgment

The chromosome studies were performed by Dr. Jack L. Titus. Dr. Robert J. Gorlin of the School of Dentistry, University of Minnesota, collaborated in the analyses of palm prints. Dr. Margery W. Shaw, M. D. Anderson Hospital, Houston, Texas, kindly reviewed the manuscript. The family pedigree and palm prints were reviewed by Dr. John Opitz, Department of Medical Genetics, University of Wisconsin, Madison.

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Routine and Change

There are, of course, in every calling, those who go about the work of the day before them, doing it according to the rules of their craft, and asking no questions of the past or of the future, or of the aim and end to which their special labor is contributing. These often consider and call themselves practical men. They pull the oars of society, and have no leisure to watch the currents running this or that way; let theorists and philosophers attend to them. In the mean time, however, these currents are carrying the practical men, too, and all their work may be thrown away, and worse than thrown away, if they do not take knowledge of them and get out of the wrong ones and into the right ones as soon as they may.—Oliver Wendell Holmes: Currents and Counter-Currents in Medical Science. Boston, Ticknow and Fields, 1861, p. 6.
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