Hereditary Factors in Atrial Septal Defect

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SUMMARY
One hundred families ascertained through a proband's having atrial septal defect (ostium secundum) were studied. Selection of certain pedigrees from the overall data could lead to the conclusion that atrial septal defect is inherited as a Mendelian dominant or a Mendelian recessive, depending on the pedigrees selected. Analysis of the overall data from this study and from the literature suggests multifactorial inheritance of atrial septal defect as the explanation most consistent with available observations. The distinction between inheritance of a defect through single factor or multifactorial modes is of more than academic interest. From the point of view of genetic counseling, the risk to the newborn is not fixed in multifactorial inheritance but increases with the number of affected relatives. From the point of view of prevention, environmental hazards such as drugs and illnesses may play an important role in the production of defects showing multifactorial inheritance.

Additional Indexing Words:
Multifactorial inheritance  Mendelian dominant or recessive  Genetic counseling
Congenital heart disease  Teratogenic hazards

The concept that diseases tend to run in families is as old as medicine and, indeed, has been traced back to Hippocrates as the doctrine of diathesis. Recently, Edwards¹ stated that "Familial concentration is a feature common to all diseases in man."

Mendelian inheritance has been useful in explaining many of the rare diseases in humans, but the majority of illnesses, particularly the common diseases, do not easily conform to simple dominant and recessive patterns.

Trying to understand the possible modes of inheritance of congenital heart disease has been both unrewarding and confusing. The same lesion may appear in successive generations of one family, simulating dominant inheritance and appear in siblings in another family, suggesting (though by no means proving) recessive inheritance. In one family there may be an associated chromosomal abnormality and in another a potentially teratogenic prenatal event of unknown significance to the cardiac malformation.

It has not proved profitable, and does not seem reasonable, to study all congenital heart diseases together as if they represent a single disease. Our present understanding of the embryology of the heart and the frequent association of certain lesions permit us to make some decisions as to what constitutes meaningful developmental groups of lesions and prohibit us from mixing, for example, endocardial cushion defects with endocardial fibroelastosis.

Our selection of a lesion suitable for intensive study was influenced by certain criteria. The lesion should be common enough to provide an adequate number of patients. It should be compatible with life into the reproductive age, and it should be a defect that is diagnosed with reasonable
ease and accuracy. Atrial septal defect (ASD) (ostium secundum), which is the most common congenital heart lesion encountered in adults, adequately fulfills these criteria.

A search of the literature finds a suggestion by Howitt that atrial septal defect may be inherited as a Mendelian dominant. It has been reported by Carleton and associates as being consistent with recessive inheritance. Campbell and Polani have suggested that atrial septal defect may be inherited as either an autosomal dominant or a recessive. Atrial septal defects have also been described in association with gross chromosomal aberrations and following a teratogenic exposure. Lamy and his colleagues have suggested that both genetic and nongenetic factors are equally important in the etiology of atrial septal defect. Clearly, efforts at defining the inheritance of atrial septal defect reflect the confusion associated with trying to describe the genetics of congenital heart diseases in general.

The following report is our attempt to find out how a representative congenital heart lesion, atrial septal defect, may be inherited.

Methods

One hundred patients, ranging in age from 3 months to 33 years, with atrial septal defect (ostium secundum), were examined on admission to the wards or outpatient clinics of the University of Wisconsin Hospitals, Madison, Wisconsin, the Texas Children's Hospital, Houston, Texas, and the Montreal Children's Hospital, Montreal, Canada. The patients were selected without prior knowledge as to their genetic backgrounds, and the diagnoses were established on the usual clinical, roentgenographic, and electrocardiographic evidence. Further confirmation was obtained from heart catheterization or surgery or both in 92 cases. Nineteen probands had in association one or more of the following: pulmonic stenosis (PS), pulmonary branch stenosis, ventricular septal defect (VSD), partial anomalous venous return, and persistent left superior vena cava.

Family histories and pedigrees were recorded, and coded on punch cards as reported in greater detail elsewhere. Reports of autopsies, local physicians' records, and death certificates were obtained in as many cases as possible. In 74 families, all living siblings and parents of the probands received a personal cardiological evaluation, and more distant relatives were examined on occasion. In 26 families, one or more of the first degree relatives were not examined.

Four members of one family having eight individuals with congenital heart defects had chromosomal studies.

Twenty-two probands were under 2 years of age, and it was felt, in these cases, that the events of the pregnancies would still be recent enough in the minds of the mothers to yield valid teratogenic histories. In 20 of these 22 patients, data on 100 selected categories of teratogenic hazards, illnesses, and drug exposures were recorded and coded on punch cards.

Results

Thirty-two of the 100 families ascertained, through a proband, as having an atrial septal defect (ostium secundum) had at least one other individual with acceptable evidence of a congenital heart lesion. During the course of the study, four previously unsuspected cases of congenital heart disease were discovered. Table 1 shows the number and relationship of the affected individuals to the probands.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Total</th>
<th>No. affected</th>
<th>% affected</th>
<th>ASD</th>
<th>ASD+ Lesion</th>
<th>No ASD</th>
<th>Unknown</th>
</tr>
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<tr>
<td>Sibs</td>
<td>279</td>
<td>10</td>
<td>3.7</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Parents</td>
<td>200</td>
<td>7</td>
<td>3.5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Children</td>
<td>8</td>
<td>0</td>
<td>0.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grandparents</td>
<td>400</td>
<td>4</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Aunts &amp; uncles</td>
<td>871</td>
<td>11</td>
<td>1.3</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>First cousins</td>
<td>1423</td>
<td>10</td>
<td>0.7</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>More distant relatives</td>
<td>1761</td>
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<td>0.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>9</td>
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<tr>
<td></td>
<td>4942</td>
<td>51</td>
<td>1.03</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 1

Frequency of Congenital Heart Diseases in Relatives of 100 Probands Having Atrial Septal Defect (ASD)
Of great interest is the finding that 10 of the 279 siblings of the index cases (3.7%) and seven of the parents of the probands (3.5%) also had congenital heart defects. Considering only diagnosed atrial septal defects, as the degree of relationship to the proband decreased, the frequency of affected individuals decreased from about 3.6% in parents and sibs to 1.2% in grandparents, uncles, and aunts, and to 0.7% in first cousins.

Of the 20 affected relatives for whom the cardiological diagnosis was established, 18 had atrial septal defects and nine of these had one or more additional heart lesions. Two relatives did not have atrial septal defects. These were the mother of one proband with ASD and pulmonic stenosis who had only pulmonic stenosis (fig. 1, pedigree 1), and a sibling of a proband with an atrial septal defect who had a ventricular septal defect (fig. 2, pedigree 2).

The excess of females over males among the probands (62:38) was significant at the 2% level \( (X^2 = 5.7) \) and is consistent with the findings of others.4 The mean parental age was 26.3 ± 3.9 years for mothers and 29.9 ± 4.8 years for fathers. The proband was the first-born in 35 pedigrees; the mean birth rank was 2.6, and the mean sibship size was 3.8. The frequency of miscarriages or spontaneous abortions among the sibs of the probands was 12.9%, reasonably close to the value of 14.7% reported for the general population.11 There were four stillbirths. Season of birth did not differ significantly from random expectation.

Associated anomalies were present in seven probands. These included hydronephrosis, skeletal anomalies of the hand (of the Holt-Oram type), strabismus, and inguinal and umbilical hernias. Information was obtained on the birth weight of 86 of the probands. Seventy-five weighed over 3,000 g, seven were in the weight range of 2,500 to 3,000 g, and four were in the range of 2,000 to 2,500 g. Thus, only 5% were premature by the common, but not entirely satisfactory, criterion of birth weight.

A history of illness or exposure to a hazard that could be considered teratogenic was elicited from 17 of the 20 mothers on whom teratogenic histories were obtained. These data will be reported elsewhere.

No twins appeared in this study. Consanguinity of the proband’s parents was reported in four families: two marriages between second cousins and two marriages between more distantly related individuals.

A description of some of the 32 families which had more than one affected individual illustrates the variability in the family distributions. Two of the seven families in our series in which a proband had a parent with a cardiac malformation are shown in figures 3 and 4.

By the criterion of direct transmission from parent to child, pedigrees 3 and 4 (figs. 3 and 4) suggest dominant inheritance. So does pedigree 6, except for one instance of transmission through an unaffected parent.
ATRIAL SEPTAL DEFECT

which, in the conventional terminology, could be interpreted as “reduced penetrance.” This family is also consistent with the criterion of a 1:1 ratio of affected to normal in the offspring of affected individuals. The literature contains a number of such pedigrees selected to support the interpretation of dominant inheritance.

Figures 2 and 5 present two pedigrees (pedigrees 2 and 5) in which siblings are affected and parents are free of disease. This familial pattern is compatible with autosomal recessive inheritance and similar pedigrees have been so interpreted in the literature. A new consideration, variable expressivity, is introduced here. In figure 5, the sister (II-3) of the proband has, in addition to her atrial septal defect, pulmonic stenosis. In figure 2, the sister (II-1) of the proband does not have ASD at all, but has a ventricular septal defect.

The pedigree in figure 1 suggests that the same genetic predisposition may indeed manifest itself in various ways. The proband has ASD and pulmonic stenosis. Her brother (II-2) has ASD, PS, and VSD. The mother (I-2) of these siblings had only pulmonic stenosis (which was severe enough to require surgical correction). Such a familial concentration of several types of cardiac malformation is not likely to be coincidental.

The most striking pedigree in the entire series is illustrated in figure 6, which reveals eight individuals with congenital heart lesions. The proband, who is 5 years old, has atrial septal defect, pulmonic stenosis, and persistent left superior vena cava demonstrated by cardiac catheterization. An older brother (IV-18), now 11 years old, also had ASD and PS which have been surgically corrected. Another brother (IV-20) died at 17 hours of age, and at autopsy the following lesions were demonstrated: ASD, pulmonary valve atresia, absent tricuspid valve and hypoplastic right ventricle. The mother (III-9), who is 30, had as her sole cardiac lesion an atrial septal defect, which has been repaired. The grandmother (II-4) died in 1938 at 35 years of age. Her death certificate records the cause of death as congenital heart disease. A maternal aunt (III-8) died in 1930 at 22 months of age with a diagnosis on the death certificate of congenital heart disease. A maternal uncle (III-7) is reported to have died in the late 1920's or early 1930's at 3 months of age, with a diagnosis of congenital heart disease.
also recorded on a death certificate, according to III-9. Although the county registrar could not locate this last death certificate, the history was still considered acceptable.

It is seen in the pedigree that the affected mother of the proband had three out of four affected children and was part of a sibship of three out of four affected sibs. The only sibling not affected in the mother's sibship is a brother (III-6) who has been personally examined and has no evidence of a congenital heart defect. However, one of his three children (IV-17) has not only atrial septal defect (on clinical, electrocardiographic, and roentgenographic grounds), but also has a cleft lip, cleft palate, mental retardation and hearing deficit.

The four living, affected members of this family had blood drawn for chromosome karyotyping. In three patients, satisfactory preparations were made and in none of these was chromosomal aberration detected.

Discussion

Is it possible to suggest a meaningful pattern of inheritance from such apparently conflicting data? Inspection of the pedigrees makes it clear that no simple mode of inheritance will account for all the familial cases, not to mention the large number of isolated cases.

Pedigrees such as those in figures 1, 3, 4, and 6 are consistent with autosomal dominant inheritance. In figure 1 variable expressivity is introduced with a mother having one lesion and two of her three children having different combinations of heart defects. Figure 6 also illustrates variable expressivity and an interesting “failure of penetrance” if the pedigree is interpreted in terms of a single gene difference. The presumptive gene appears to be fully penetrant by genetic ratio in generations III and IV, yet it curiously spares III-6 and reappears in IV-17.
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Certainly if all the pedigrees were like those in figures 1, 3, 4, and 6, autosomal dominant inheritance would be the most reasonable interpretation. However, only seven of the 200 parents of the probands (3.5%) were affected. For fully penetrant dominant inheritance, the expectation would be one affected parent for each of the 100 probands. This requires the unsatisfactory assumption that the gene has a penetrance of only 7%.

Selected families such as the one presented in figures 2 and 5 offer another possible explanation. Affected siblings, the offspring of parents known to be free of congenital heart disease, presenting in a genetic ratio which approximates a one in four expectation, suggest autosomal recessive inheritance. Yet looking beyond the single pedigrees to the overall data obtained from the sample of 100 families, an incidence of 3.7% of affected siblings falls so far short of a one in four expectation that this hypothesis must be rejected.

It was pointed out by Wright in 193412 and more recently by Edwards1 that Mendelian inheritance can sometimes be simulated by a system in which an underlying process, controlled by a large number of genes each with a relatively small effect (multifactorial inheritance), is related to a biological threshold, such that all the individuals on one side of the threshold are unaffected and on the other side are affected with the trait in question. Mental retardation is an example, where the threshold is arbitrarily imposed at an IQ of 70 on a continuous distribution of "intelligence." It has been shown that palate closure and cleft palate may fall into this category, named “quasi-continuous variations” by Gruneberg.13 If the palate shelves do not move from the vertical to the horizontal plane by a given stage of development, they are unable to meet and fuse, and the embryo will have a cleft palate.14

A number of authors have discussed the problem of quasi-continuous variations in man, and how this may be distinguished from other modes of inheritance.1, 15–17 Such traits tend to be relatively common abnormalities (for example, 1 to 0.1%), to show a familial tendency (with a recurrence rate in sibs of about 1 to 5%), to show deviations from the normal sex ratio, and to show evidence of response to environmental influences such as variation in frequency with season of birth parental age, birth rank, socio-economic class, and geographical distribution.

Atrial septal defect falls into the appropriate frequency range, shows a familial tendency, has a recurrence risk of 3.7% in siblings, and affects more females than males. Associations with parental age, birth order, season of birth, and socio-economic class were not revealed by our data, but since we did not have critical controls for these factors, small variations cannot be ruled out.

Edwards1 has calculated that threshold traits showing multifactorial inheritance with a population frequency of p are expected to show a frequency of \(\sqrt{p}\) for the trait in the first degree relatives (parents and sibs) of affected individuals, and Newcombe17 has plotted this relationship for a number of pathological conditions.

Precise estimates of the population frequency of atrial septal defect (ostium secundum) are unfortunately not available. Richards and associates18 found that 0.7% of live births in an American series had congenital heart defects, and the figures reported by Nadas19 show that about 10% of all congenital cardiac malformations are atrial septal defects. The population frequency of atrial septal defect can thus be estimated as about 0.07%, and the expected frequency of the defect in parents and sibs would be \(\sqrt{0.0007}\), or 0.026, which is reasonably close to the observed figure of 0.036 (table 2). A similar calculation based on an estimate of the frequency of congenital heart disease in Great Britain reported by MacMahon and associates20 and Campbell and Polani's4 estimate of 1.1% for the recurrence risk of ASD in the siblings of probands also give reasonable agreement with expectation (table 2).

Another way to look at these data is to plot the information on the graph devised by Newcombe17 as shown in figure 7. In both
Table 2

Comparison of Frequency of Occurrence of Atrial Septal Defects with Expected Frequency in First Degree Relatives in Multifactorial Inheritance

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Estimate of ( p )</th>
<th>Expected ( 1/p )</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibs (this study)</td>
<td>0.0007</td>
<td>0.026</td>
<td>0.037</td>
</tr>
<tr>
<td>Parents (this study)</td>
<td>0.0007</td>
<td>0.026</td>
<td>0.035</td>
</tr>
<tr>
<td>Sibs (literature)</td>
<td>0.00032 (MacMahon et al.(^ {20} ))</td>
<td>0.0179 (MacMahon et al.(^ {20} ))</td>
<td>0.011 (Campbell &amp; Polani(^ {4} ))</td>
</tr>
</tbody>
</table>

Figure 7

Ratio of frequency in siblings to that in general population for multifactorial single recessive and single dominant inheritance (after Newcombe\(^ {17} \)) including present data.
sets of data atrial septal defect falls close to the line for multifactorial inheritance. This study places ASD slightly above the line, while analysis of the British data puts ASD just below the same line. Considering the variables involved, the agreement is surprisingly good.

There is more involved here than merely an exercise in juggling numbers. From the point of view of genetic counseling and possible prevention, there is a difference between the inheritance of a defect through a single factor and a multifactorial system.

When the defect is determined by a single gene difference, the risk to the unborn can be predicted from the Mendelian laws and does not change with successive children, but in a multifactorial system, the risk to the unborn increases with the number of relatives affected. In an autosomal recessive system the risk to every unborn sibling of an affected child remains one in four. In a multifactorial system the average risk for the sibling may be predicted from the square root of the population frequency but varies from family to family. If atrial septal defect is the result of multifactorial inheritance, a mother who has delivered a child with atrial septal defect could be counseled that, if she and her husband have no other close relatives with congenital heart lesions, the risk to future unborn children would be approximately 2.6%. However, if they have affected parents, siblings, or other children, the risk to the unborn increases, since the affected relatives are an indication that they are likely to have inherited more of the genes predisposing to the defect than parents with a negative family history. Just how much the risk is increased after two affected children have been born is still unknown. Arguing by analogy from cleft lip,21 and spina bifida or anencephaly, or both 16, it seems that the risk for subsequent children is about doubled (that is, from these data to about 7%). In the case of pedigree 6 (fig. 6), however, the mother herself was affected, and this would increase the risk still further (perhaps to 15 or 20%).

It should not be assumed that if atrial septal defect is a multifactorially determined threshold character, the role of the environment can be neglected. A number of teratological experiments have demonstrated that if the embryo's genotype places it near the threshold a relatively small environmental "insult" may be enough to move the individual beyond the threshold and produce a defect.22 Thus, in pregnancies where there is a history of congenital malformations in near relatives, particular care should be taken to protect the developing embryo from avoidable environmental agents, such as unnecessary drugs.

Although atrial septal defect (ostium secundum) can be produced by a single mutant gene, as in the Ellis-van Creveld syndrome,23 by a chromosomal anomaly, as in the D, E, and G syndromes, or by an environmental teratogen such as rubella, a synthesis of observations from the literature with the results of this study leads us to suggest that the majority of cases represent multifactorial inheritance of a threshold character.

References


Pulsatile Pulmonary Blood Flow—Suggestion by Harvey, 1628

In the liver there is no impulsive, no strength forcing; in the lungs the blood is thrust against them by the impulsion of the right ventricle of the heart, by which impulsion there must necessarily follow a distention of the vessels and porosities of the lungs. Besides, the lungs in respiration rise and fall (Galen, De Usu Partium), by which motion it follows of necessity, that the porosities of them and their vessels are open'd and shut, as it falls out in sponges, and all things of a spongy substance when they are constricted and dilated again.—The Anatomical Exercises of Dr. William Harvey: D Motu Cordis 1628; De Circulatione Sanguinis 1649 (first English text). Edited by Geoffrey Keynes. London, The Nonesuch Press, 1653, p. 50.
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