Possible X-Linked Congenital Heart Disease

By Patricia L. Monteleone, M.D., and Leonard F. Fagan, M.D.

SUMMARY

Four male members of a family are known to have congenital mitral and aortic insufficiency, a fifth male has congenital mitral insufficiency only, and a sixth male had congenital heart disease by history. The involved males comprised all males in three generations of this family. Chromosomal and dermatoglyphic studies of the two living affected males are normal.

The involvement of males in this family is best explained on the basis of X-linked recessive inheritance. To our knowledge, this is the first report of possible X-linked inheritance of isolated congenital heart disease.

Additional Indexing Words:
Mitral insufficiency  Aortic insufficiency  Tricuspid insufficiency
Dermatoglyphic studies  Chromosomal studies

While the cause of most congenital heart disease is usually unknown, some lesions are now known to result from intrauterine infections or to be associated with metabolic disorders, for example, nonfamilial supravalvular aortic stenosis and hypercalcemia.

The genetic basis of congenital heart disease is also well established for a few anomalies such as those associated with chromosomal abnormalities. Single gene inheritance has been postulated as the mode of transmission for endocardial fibroelastosis, muscular subaortic stenosis, idiopathic familial myocardopathy, and familial supravalvular aortic stenosis. It has been suggested that hereditary ventricular hypertrophy is inherited as an autosomal dominant while Weil and Allenstein proposed that atrial septal defect may be inherited as an autosomal dominant with a varying degree of penetrance. It has also been suggested that a recessive form of inheritance is present in many families with endocardial fibroelastosis. While autosomal dominant and autosomal recessive modes of inheritance have been proposed, to date, no instance of isolated congenital heart disease with an X-linked mode of transmission has been reported. We have studied three generations of a family, four male members of which have mitral insufficiency and aortic insufficiency and two of the four had associated tricuspid insufficiency. One additional male member has only mitral insufficiency. A sixth male member is said to have expired with congenital heart disease, but his records are not available. The mode of inheritance seems to be X-linked recessive from the pedigree which is shown in figure 1.

Report of Cases

Patient J.J. (III-7)

This patient, the propositus, was first seen in our cardiology clinic at 12 years of age because of dizzy spells and pains in the lower extremities. He had signs and symptoms consistent with congenital heart disease since birth, which the mother was aware of, but the child was not followed by a physician consistently. The boy was a well-developed, well-nourished Negro with a III/VI high-pitched systolic murmur and a II/VI high-pitched diastolic murmur starting at the second heart sound along the left sternal border. Blood pressure was 150/30 with an enlarged bounding aorta felt from the xiphoid to the umbilicus and prominent pulses in the neck and peripherally with pistol shot sounds. Roentgenogram of the
chest showed cardiomegaly with prominence of the pulmonary trunk. The electrocardiogram revealed left ventricular and left atrial hypertrophy. Cardiac catheterization data are shown in table 1. Cineangiograms confirmed the clinical diagnosis of mitral insufficiency and aortic insufficiency.

**Patient M.J. (III-9)**

This patient was first seen by us at 7 years of age because of a murmur detected on routine examination by a physician. The child showed signs and symptoms of congenital heart disease since birth but was not taken to a physician by his parents. He was a well-developed male with a high-pitched holosystolic murmur at the apex and an inflow diastolic murmur consistent with mitral insufficiency. Blood pressure was 120/70 and peripheral pulses were normal. Roentgenogram of the chest showed left atrial and left ventricular enlargement. Electrocardiogram revealed left atrial hypertrophy and left ventricular dominance. Cardiac catheterization data are shown in table 1. A cineangiogram confirmed the clinical diagnosis of mitral insufficiency.

**Patient A.L. (III-1)**

The patient was diagnosed and followed in the cardiology clinic at another hospital with numerous admissions for 15 years. He was known to have congenital heart disease since birth and was followed by numerous physicians prior to entry into the cardiology clinic. He was admitted to that hospital for surgery at 29 years of age because of complaints of shortness of breath, leg pains, and headaches. Auscultation of the heart revealed a III/VI holosystolic murmur and a IV/VI aortic diastolic murmur consistent with mitral insufficiency and aortic insufficiency. Blood pressure was 160/40; the carotid arteries and other peripheral arteries showed bounding pulsations. Roentgenogram of the chest showed cardiomegaly with enlargement of both right and left chambers. A vectorcardiogram was consistent with left ventricular hypertrophy. Cardiac catheterization results are shown in table 1. It is unusual to find a left ventricular end-diastolic pressure of 0 in a patient with mitral insufficiency, but this was documented from examination of the original data. Cineangiograms revealed mitral, aortic, and tricuspid insufficiency. Cardiovascular surgery was performed and a prosthetic aortic valve was inserted, but the patient expired a few hours following surgery.

At autopsy the heart was markedly enlarged, and an antemortem thrombus was attached to the artificial valve. Surgical absence of the aortic valve with replacement by an artificial prosthetic valve was noted. The leaflets of the mitral and tricuspid valves were elongated, soft, and redundant with focal nodules of myxomatous tissue and numerous fenestrations. Acute fibrinous pericarditis was observed as well as a massive pericardial effusion.

Microscopically, the lungs showed marked congestion and edema with partial atelectasis of the lower lobes. The valves showed myxomatous degeneration of the leaflets and they lacked their usual rigidity. This case was stated to be a good example of the "floppy valve syndrome" described by Read and others. No microscopic evidence of rheumatic heart disease was found. Likewise, there was no evidence of primary idiopathic myocardial disease in this patient.

**Figure 1**

Pedigree of family with suspected X-linked congenital heart disease. Arrow points to propositus (Patient J.J., III-7).
Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Catheterization pressures (mm Hg)</th>
<th>Catheterization Data Including Pressures and Cineangiograms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.L. (III-1)</td>
<td>20†</td>
<td>LV: 160/0</td>
<td>Right and left, ‡ cineangiograms: 15‡</td>
</tr>
<tr>
<td>C.L. (III-2)</td>
<td>15‡</td>
<td>120/0-8</td>
<td>No‡</td>
</tr>
<tr>
<td>J.J. (III-7)</td>
<td>12</td>
<td>1</td>
<td>Right, cineangiograms: 30-3</td>
</tr>
<tr>
<td>M.J. (III-9)</td>
<td>7</td>
<td>1</td>
<td>Right, cineangiograms: 30-3</td>
</tr>
<tr>
<td>O.H. (IV-1)</td>
<td>8/12‡</td>
<td>8/12‡</td>
<td>Right, cineangiograms: 30-3</td>
</tr>
</tbody>
</table>

* Inf. sten. = infundibular stenosis.
† Expired.
‡ Washington University School of Medicine.
§ Clinical diagnosis only.

Patient C.L. (III-2)

Patient C.L. was followed from childhood in the cardiology clinic at another hospital and had numerous admissions for congenital heart disease. He entered that hospital in 1951 at 15 years of age complaining of dizziness and headaches. Auscultation of the heart revealed a diastolic murmur at the base of the heart with both a diastolic and a systolic murmur at the apex consistent with aortic insufficiency and mitral insufficiency. Blood pressure was 98/20 and prominent peripheral pulses with pistol shot sounds were noted. Roentgenogram of the chest showed marked enlargement of both right and left ventricles and the left atrium. Electrocardiogram showed premature contractions and left atrial, left ventricular, and right ventricular enlargement. No cardiac catheterization studies were done. The patient developed atrial fibrillation and expired shortly after entering the hospital. No autopsy was permitted.

Patient O.H. (IV-1)

This patient, the 8-month-old offspring of III-3, was diagnosed as having congenital heart disease shortly after birth in 1951 at another hospital. He was followed in the cardiology clinic at that hospital and re-entered at 8 months of age because of difficulty in breathing. Physical examination revealed a III/VI harsh, blowing systolic murmur and a questionable to-and-fro murmur, consistent with mitral insufficiency. No blood pressure was recorded. Roentgenogram of the chest showed left atrial and left ventricular enlargement. Electrocardiographic findings were within normal limits. No cardiac catheterization was performed. The baby expired at 8 months of age. Autopsy was not permitted.

A maternal uncle, II-1, was said to have expired several years ago at 25 years of age of "congenital heart disease." No details of the uncle's condition were available.

Chromosomal analyses performed on patients J.J. and M.J. (III-7 and III-9) showed normal male karyotypes. Dermatoglyphics likewise were within normal limits for both patients.

The Family

Hospital records of the entire family were extensively and carefully reviewed. There is no family history of rheumatic fever or of symptoms suggestive of rheumatic fever in any of the family members questioned. All of the female members of this family were examined by a private physician, and none showed heart disease. Their ages are 26, 18 (twins), 15, and 8 years and 8 months, respectively. Repeated inquiry failed to reveal a consanguineous relationship between the parents of any affected members. Pa-
tient II-2 had two sets of stillborn twins, and it is not known whether any heart defects were present. She likewise had two abortions in the first trimester.

Discussion

We are aware of no reports of X-linked inheritance of isolated congenital defects of the heart. It is documented by history and available records that the heart disease is congenital in the affected members, and there was no evidence of rheumatic disease or primary idiopathic myocardial disease in patient III-1 at necropsy or in any of the family members (affected and unaffected) clinically.

Valvular lesions similar to those found in patient III-1 at autopsy have been described in Marfan's disease and other mesodermal dystrophies. This lesion may be responsible for a significant incidence of valvular insufficiency which in the past has been erroneously included with the manifestations of rheumatic disease. Ophthalmological examination was performed on the living affected patients, and there was no evidence of ectopia lentis. In addition, there were no physical findings consistent with Marfan's disease.

The fact that only male members of the family are affected suggests an X-linked type of inheritance. Although one would expect only one half of the males in generation III to be affected and one half of the females to be carriers, the appearance of the defect in all four males of that generation is not statistical-ly unlikely. It is conceivable that the lesions are the result of dominant inheritance with sex limitation; in general, however, a sex-limited manifestation occurs only in functions or organs which normally exhibit distinct sexual characteristics. Only if living involved males have similarly involved sons could dominant inheritance with sex limitation be proven. We feel that the anomalies of the heart in this family are probably best explained on the basis of an X-linked recessive transmission.

Acknowledgment

The authors wish to thank Miss Joan Grzegocki and Mrs. Julia Durst for cytogenetic technical assistance, Barnes Hospital and St. Louis Children's Hospital for their assistance in review of records, and Mrs. Charlotte Hill for help with the manuscript. We wish to thank Brent Parker, M.D., and David Goldring, M.D., for permitting us to review records of their patients.

References

Possible X-Linked Congenital Heart Disease
PATRICIA L. MONTELEONE and LEONARD F. FAGAN

Circulation. 1969;39:611-614
doi: 10.1161/01.CIR.39.5.611
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1969 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/39/5/611

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/