Cardiac, Skeletal and Ophthalmologic Abnormalities in Relatives of Patients with the Marfan Syndrome

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SUMMARY Nine patients with the Marfan syndrome and 40 of their first degree relatives were evaluated for the presence of cardiac, skeletal and ophthalmologic abnormalities. Aortic root dilatation and mitral valve prolapse were sought by echocardiography, and the metacarpal index was calculated from hand X-rays. Abnormalities of all the tests performed were present in all nine index cases, except for one normal eye exam. Mitral prolapse was present in thirteen relatives (33%) and aortic root dilatation in seven (18%). At least one cardiac abnormality was present in nineteen (47%) relatives. Aortic root dilatation was more common in male relatives; the incidence of mitral prolapse was approximately equal in the two sexes. Abnormal metacarpal index (greater than 8.0) occurred in fifteen of twenty-six relatives examined (58%). Ophthalmologic abnormalities were found in only four relatives. Two relatives had abnormalities of all three organ systems evaluated, five others had abnormalities of two systems, and fourteen had abnormalities of one system. We conclude that cardiac and skeletal abnormalities are demonstrable in a high percentage of first degree relatives of patients with the Marfan syndrome.

THE MARFAN SYNDROME is a genetically determined disorder of connective tissue. The disease is transmitted as an autosomal dominant trait, with high penetrance and variable expressivity. The clinical presentation of the Marfan syndrome is variable; when complete it includes arachnodactyly, high arched palate, other skeletal abnormalities, ectopia lentis, lack of subcutaneous tissue and loss of muscle bulk. The common cardiovascular manifestations of this syndrome include cystic medial degeneration of the great vessels, particularly of the ascending aorta, which results in dilatation, dissection or aneurysm formation with or without aortic valve regurgitation, and mitral valve prolapse and regurgitation.1

The prevalence of aortic root dilatation and mitral valve prolapse abnormalities in patients with the Marfan syndrome has been studied by Brown et al. using echocardiography.3 However, although the condition is familial, the incidence of cardiovascular involvement in relatives of patients with the Marfan syndrome has not been extensively studied. Nor has the presence of cardiovascular involvement in relatives been compared with the incidence of skeletal and ophthalmologic abnormalities.

The purpose of this study was to determine and compare the frequency of cardiovascular, skeletal and ophthalmologic abnormalities in patients with the Marfan syndrome and in their first degree relatives.

Methods

The files of the University of Iowa Hospitals were reviewed to identify all patients with the diagnosis of the Marfan syndrome. The diagnosis in these patients was made originally by ward or clinic physicians on clinical grounds, usually because of varying combinations of skeletal, cardiac and ophthalmologic abnormalities.1 Attempts to contact all these patients by letter and telephone were made; nine patients agreed to return for further studies, and were accompanied by at least two first degree relatives each. A tenth patient had died since the original diagnosis was made, but her family was studied. Thus a total of ten kindreds, consisting of nine index cases and forty first degree relatives, was studied. No attempt was made to preselect the patients or their relatives. This project was approved by the University of Iowa Human Research Committee, and informed consent was obtained from all participants.

Cardiac Evaluation

All patients and relatives underwent a complete history and physical examination. Electrocardiograms and chest PA and lateral X-rays were performed. Echocardiograms were obtained on all relatives and patients, in the supine or slight left lateral decubitus position using a Smith-Kline Ekoline 20A ultrasonicoscope and a 2.25 MHz transducer focused at 7.5 cm. Recordings were made on a Honeywell 1856 fiberoptic strip chart recorder. Standard scanning techniques to visualize the left ventricle, mitral valve and aortic root were employed. The mitral valve recordings were obtained with the transducer perpendicular to the chest wall, usually in the third or fourth interspace. In one relative no satisfactory mitral echograms could be obtained with the transducer in this position and angulation; this subject was not included in the study. Numerous descriptions of mitral valve prolapse on echocardiograms are available.4,5 In this study we adopted the criteria of Markiewicz et al.,7 which correlated well with the presence of mid-systolic clicks and late systolic murmurs. The points of coaptation (C point) and separation (D point) of the mitral valve leaflets were identified and a line drawn between the two (CD line). Prolapse was considered to be present if the predominant systolic mitral echo extended more than 2 mm posteriorly from the CD line, either in a smooth concave hammock-shaped fashion (holosystolic prolapse, fig. 1) or as a sharp mid-late systolic buckling (mid-systolic prolapse, fig. 2). The aortic root dimension was measured from the most anterior echo of the anterior aortic wall to the most anterior echo of the posterior aortic wall, at end diastole (figs. 3 and 4). Aortic root measurements were made only from echocardiographic recordings where at least

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Received December 19, 1975; revision accepted December 10, 1976.
a portion of the aortic valve echo was also visible. The left atrial dimension was measured from the most anterior echo of the posterior aortic wall to the most anterior echo of the left atrial wall, at end systole (figs. 3 and 4).

Aortic root enlargement was determined using the criteria of Brown et al. For adults we required that the aortic dimension be abnormally large by at least two of the following three criteria: greater than 3.7 cm in diameter, or greater than 2.2 cm/m² of the body surface area, or a left atrial dimension/aortic root dimension ratio of 0.7 or less. However, in the case of three individuals whose left atrial dimension was enlarged the third criterion was not used; the aortic root was considered large only if both the first and second criteria were fulfilled. For children (less than 16 years old) the numerical criteria were modified by age and weight.

Left atrial enlargement was considered to be present in adults if the absolute size exceeded 4.0 cm, or 2.1 cm/m² of body surface area. Children were considered to have left atrial enlargement if the measured dimension exceeded 2.7 cm (25–50 lbs), 2.8 cm (50–75 lbs) or 3.0 cm (75–100 lbs). If the child’s weight was over 100 lbs, adult criteria were used.

Ophthalmologic examination, including slit-lamp and gonioscopy, was performed in seven of the nine living index cases, and in 28 of the 40 relatives. We looked specifically for the following findings which have been reported to occur in the eyes of patients with the Marfan syndrome: ectopia lentis, reduced visual acuity, myopia, astigmatism, ocular deviation, blue sclerae, large or small corneas, small pupils, failure of pupils to dilate, persistent pupillary membranes, iris heterochromia, iris translucency, iris stromal hypoplasia, spherophakia, lens opacities, glaucoma, chamber angle abnormalities (numerous thick iris processes or pectinate ligaments, mounds of mesodermal tissue, abnormally kinked or coiled segments of the greater iris arterial circle, and thinning of iris mesoderm at the iris root exposing the pigment epithelium to form dark scallops or palisades), peripheral retinal degenerations or tears, and retinal detachment.

No single abnormality or combination of abnormalities noted on an ocular examination is specific or diagnostic enough to positively identify a patient as having the Marfan syndrome. We classified our subjects as having probable,
possible or no ocular signs of the Marfan syndrome. Subjects
with subluxed lenses and anterior chamber angle abnor-
malities were classified probable. Subjects with normal
lenses who had anterior chamber angle abnormalities were
classified possible. Some subjects had other ocular abnor-
malities (myopia, astigmatism, esotropia or lattice degenera-
tion) which occur frequently in conjunction with the Marfan
syndrome; we felt these abnormalities are too prevalent in
the general population to be of diagnostic significance.

Skeletal abnormalities were sought by using an objective
assessment — the metacarpal index. Hand X-rays in the
PA position were obtained in six patients and twenty-six
relatives. In each subject the length of the 2nd through 5th
metacarpal bones of the right hand was measured in the
center of the bone. Each bone’s width at the midpoint was
also measured (fig. 5). The length divided by width is the
metacarpal index; this was calculated for each bone and the
four metacarpal bones measured were then averaged to yield
a single index for each subject. Sinclair et al. found that
the metacarpal index ranged from 5.5 to 8.0 in 100 normal sub-
jects, and from 8.5 to 10.5 in twenty patients with the Mar-
fan syndrome. For this investigation we considered a metacarpal index of 8.1 or greater to be abnormal, and also
noted separately those patients and relatives whose meta-
carpal index exceeded 8.4.

Results

Patients with the Marfan Syndrome (table 1)

On physical examination seven of the nine index cases had
a midsystolic click and/or mid-late systolic murmur. Only
one patient had a grade II/VI early diastolic murmur of aort-
ic regurgitation. In another patient aortic valve replacement
had previously been done for aortic regurgitation.

Chest X-ray was abnormal in three of nine patients: a
prominent aortic arch in one, severe scoliosis with left atrial
and left ventricular enlargement in another and a dilated left
atrium in a third.

The electrocardiogram was abnormal in three of nine
patients: nonspecific T wave changes in inferior leads in one,
left axis deviation in one, and severe left ventricular hyper-
trophy with strain and left atrial enlargement in one.

Echocardiography revealed prolapse of the mitral valve in
all nine patients studied. Eight showed holosystolic mitral
prolapse; in one midsystolic prolapse was present (fig. 2).

The sex distribution of these nine patients with prolapse was
five female and four male; four were children and five adults.
The left atrial dimension was abnormal in only one patient,
who had a loud mitral regurgitation murmur and mitral
prolapse on echo.

The aortic root dimension was enlarged in five of the nine
patients: three males and two females, three children and two
adults. Two of these patients had no auscultatory or radiologic evidence of aortic valve disease. Of the other three
with a dilated aortic root by echo one each had an aortic

![Figure 5. Hand X-ray in a first degree relative, illustrating the
length and width measurements made to calculate the metacarpal
index. The index is high (9.3).](http://circ.ahajournals.org/)

### Table 1. Patients with the Marfan Syndrome

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Auscultation</th>
<th>Echocardiography</th>
<th>Ophthalmologic abnormalities</th>
<th>Metacarpal index</th>
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<td>++</td>
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<td>--</td>
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Abbreviations: M = Male; F = Female; C = Systolic click; MR = Mitral regurgitation murmur; AR = Aortic regurgitation murmur; ++ = Probable Marfan syndrome; + = Possible Marfan syndrome; 0 = No Marfan syndrome (see text); -- = Not examined.
regurgitation murmur, a prominent aortic arch on X-ray and previous aortic valve replacement.

**Ophthalmologic abnormalities** were detected in six of the seven Marfan patients examined. Three of these were classified as probable Marfan syndrome, and three possible. The metacarpal index was abnormal (greater than 8.0) in all of the six index cases who had hand X-rays; five of the six had an index exceeding 8.4. Thus, of the six index cases undergoing all three special examinations (echocardiography, ophthalmologic examination and X-rays for metacarpal index) five had abnormalities on all three examinations and one had abnormalities on two. One additional patient had prolapse and ophthalmologic abnormalities (hand X-rays not obtained). Of the remaining two who had echocardiography both had mitral prolapse and one had an enlarged aortic root.

**Relatives of Patients with Marfan Syndrome (table 2)**

None of these relatives had symptoms related to the cardiovascular system, and none had a grossly abnormal (unusually tall or thin) appearance.

**Table 2. Relatives of Patients with the Marfan Syndrome**

<table>
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<th>Relatives</th>
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**Abbreviations:** S = sibling, P = parent, C = child.
the echocardiogram revealed mitral prolapse and both had mitral regurgitation murmurs.

The aortic root dimension was enlarged in seven relatives (fig. 4). None of these had aortic murmurs; one had mild dilatation of the ascending aorta on chest X-ray. Of these seven relatives, five were male and two female; four were children and three adults.

Echocardiographic abnormalities of the mitral valve and/or aortic root were encountered in at least one member of nine of the ten kindreds studied.

**Ophthalmologic abnormalities** were detected in only four of the twenty-eight relatives examined; one was classified as probably Marfan and three as possible Marfan. Two of these four relatives also had mitral prolapse. The *metacarpal index* was greater than 8.0 in fifteen (4 males and 11 females) of twenty-six relatives studied; of these it exceeded 8.4 in eight relatives (two males and six females). Seven of these fifteen relatives also had mitral prolapse. Ophthalmologic and skeletal abnormalities were associated — three of the four relatives who had ophthalmologic abnormalities had a metacarpal index exceeding 8.0. Of the three special evaluations performed (echo, ophthalmologic, metacarpal index) two relatives showed abnormalities on all three, and five more had abnormalities on two of the three.

**Discussion**

The great majority of cases with the Marfan syndrome are familial; McKusick1 has estimated that as few as 1.5% are the results of new mutation. In previous studies evaluation of relatives of cases coming to medical attention has led to the discovery of additional affected members.18 However, limited information is available with regard to the incidence of abnormalities in relatives of patients with the Marfan syndrome. Using echocardiography, a more sensitive technique for cardiac evaluation than those previously available, we found evidence of mitral prolapse in 33% of first degree relatives. Aortic root dilatation was present in 18%. Nineteen of the 40 relatives (47%) had at least one of these cardiac abnormalities. Echocardiography thus shows cardiac involvement exists in a substantial proportion of relatives of patients with the Marfan syndrome, even though cardiac symptoms are absent. In a number of these relatives cardiac involvement would have gone undetected by traditional diagnostic methods. For example, of the 13 relatives with echocardiographic evidence of prolapse only six had either mid-systolic clicks or murmurs of mitral regurgitation; of the seven with aortic root dilatation none had murmurs of aortic regurgitation and only one had a chest X-ray suggestive of aortic dilatation. In their study of patients with the Marfan syndrome, Brown et al.8 also emphasized the insensitivity of auscultation in detecting mitral valve prolapse. Likewise, the utility of the chest X-ray is limited; dilatation of the aortic root or sinuses of Valsalva is difficult to recognize on a plain chest X-ray since the cardiac silhouette obscures these structures.5,8

The Marfan syndrome patients themselves have an even higher incidence of mitral prolapse and aortic root dilatation. In this study we demonstrated mitral valve prolapse by echocardiography in 100% of our Marfan patients, and aortic root enlargement in 56%. These results are similar to those of Brown et al.8 who studied a large number of Marfan patients by echo and who found prolapse in 91% and aortic root dilatation in 60%. These workers did not study relatives of patients with the Marfan syndrome.

Previous investigators have pointed out the tendency of male patients with the Marfan syndrome to have aortic root involvement, while mitral valve involvement is found somewhat more often in female patients.2,11 Similar tendencies also exist in first degree relatives of Marfan patients, especially with regard to the aortic root. Eight of 23 (32%) of the female relatives and five of 17 (29%) of male relatives had mitral prolapse; five of 17 (29%) of the male relatives had aortic root dilatation, but only two of 23 (9%) female relatives showed dilated aortic roots ($P < 0.05$).

We also examined the relationship of the observed cardiac abnormalities to age. Fourteen of the relatives were less than 16 years old. Six of these children (36%) had mitral prolapse, as did seven of the 26 adults (27%). Thus, mitral prolapse does not make its initial appearance later in life, although it conceivably may become worse. Four of the 14 children (29%) had aortic root dilatation, but only three of the 26 adults (12%) did so. This considerably higher incidence in children may be due to an impaired life expectancy in those who have aortic root dilatation, due presumably to their increased tendency to aortic regurgitation, dissection or rupture.13-18 It may also be due to the possibility that a proportion of the index cases were new mutations, and their adult siblings and/or parents would not be affected. False paternity is another possibility for a sporadic case.

Skeletal and ophthalmologic abnormalities were as frequent as cardiac ones in the patients with the Marfan syndrome; of the seven index cases undergoing these evaluations abnormalities were uniformly present, except for one normal ophthalmologic examination. Thus the original Marfan diagnoses, made on varying clinical grounds in these patients, were supported by the additional tests we performed. Of the relatives, fifteen of 26 examined (58%) had a metacarpal index higher than the normal range determined by Sinclair et al.,13 eight of these fifteen had an index exceeding 8.4, which Sinclair et al. found only in Marfan patients. Ophthalmologic abnormalities were much less common in relatives, however, occurring in only four of twenty-eight (14%). When the ophthalmologic findings were abnormal they tended to be accompanied by a metacarpal index of greater than 8.0 (three of four relatives) and by mitral prolapse (two of four relatives). Similarly, a metacarpal index of greater than 8.0 was accompanied by mitral prolapse about half the time — in seven of fifteen relatives.

Do some of these relatives in fact have the Marfan syndrome? Two of the relatives had detectable abnormalities on each of the echocardiographic, ophthalmologic and metacarpal studies, and five other relatives had abnormalities on two of these three special tests. This group of seven relatives might reasonably be considered to have at least a *forme fruste* of the syndrome (none had a grossly abnormal external appearance, obvious chest deformities or were unusually tall or thin). One other relative had both mitral prolapse and an enlarged aortic root, and also might be considered a
forme fruste. Five more relatives had only mitral prolapse. Since prolapse may be common, and since the mitral prolapse syndrome itself has been shown to be familial, it appears that there is insufficient evidence to consider the latter group as having the Marfan syndrome. The significance of a relative having a metacarpal index exceeding 8.0 (seven subjects) without cardiac or eye abnormalities or having isolated ophthalmologic abnormalities (one subject) is not established by this study.

Of concern to the affected relative are the prognostic, therapeutic and genetic implications of some of these findings. Aortic root dilatation, as noted, may be a precursor of aortic regurgitation. Mitral prolapse may progress to hemodynamically significant mitral regurgitation in some cases. Relatives with either echo abnormality should be examined at regular intervals in order to detect the development of hemodynamically significant valvular incompetence. Probably they should also be advised of the genetic implications. If any of the cardiac, skeletal or ophthalmologic abnormalities do represent mild expression of the Marfan syndrome, then the relatives' offspring are at a 50% risk of having the genetic abnormality, with the chance that its expression might be more severe.

Another question concerns the association of bacterial endocarditis with the Marfan syndrome. The high incidence of prolapse in Marfan patients and their relatives may predispose to endocarditis; it may be that such individuals with demonstrated mitral prolapse should receive antibiotic prophylaxis to prevent the development of endocarditis. If a murmur of mitral regurgitation is present, the indications for this therapy are even stronger. Finally, in the hope of preventing rupture or dissection of the abnormal aorta, Halpern et al. have administered propranolol prophylactically to Marfan patients; the diminished myocardial contractility and slower rate of rise of aortic pressure should reduce stress in the abnormal and weakened aortic wall. If this therapy proves effective in reducing the rate of dissection or rupture, it may be appropriate to similarly treat Marfan relatives who have dilated aortic roots on echo.

Acknowledgment

We are indebted to Dr. Kenneth C. Kaplan who obtained echocardiograms on one kindred, to Ms. Phyllis Shellady and Ms. Linda Rath for expert technical assistance, and to Ms. Diane Phillips for expert secretarial aid.

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Circulation. 1977;55:797-802
doi: 10.1161/01.CIR.55.5.797
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 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:
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