Cardiovascular Malformations and Complications in Turner Syndrome

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ABSTRACT. *Background.* **Turner syndrome (gonadal dysgenesis with sex chromosome abnormalities) is recognized to be a disorder in which cardiovascular malformations are common. The prevalence and natural history of these findings, the risk for aortic dissection, and the occurrence of cardiovascular disease have all been the subject of debate, as have been the American Academy of Pediatrics recommendations for cardiac screening of patients with Turner syndrome.**

Objective. **To evaluate a large population of patients both cross-sectionally and longitudinally to determine the prevalence of cardiovascular malformations, the risk for dissection of the aorta, to determine whether there are phenotype:karyotype correlations that can allow for specific recommendations, and to devise an appropriate screening protocol.**

Design and Methods. **Data have been collected for patients with Turner syndrome. These individuals have been seen in an ongoing clinic established for the study of the natural history of Turner syndrome. Data from physical examinations, evaluations by cardiologists, echocardiography results, medical and surgical complications, medical records, and causes of death were analyzed. A total of 244 of 462 individuals in this population with karyotype-proven Turner syndrome could be evaluated because echocardiograms had been obtained. In addition, the medical literature was reviewed for occurrences of aortic dissection in patients with Turner syndrome.**

Results. **A total of 136 (56%) of 244 of these patients had cardiovascular abnormalities, 96 (71%) were structural, 40 (29%) were functional, including hypertension (HBP), mitral valve prolapse and conduction defects. Coarctation of the aorta and bicuspid aortic valve, alone or in combination, comprised >50% of the cardiac malformations. Bicuspid valve was often not detected by examination, but only by echocardiography. Aortic dissection occurred in three of the patients. In one, it was traumatic; in a second, it occurred at the site of coarctation repair. The third patient had long-standing HBP with malignant obesity. In the literature, there have been 42 case reports of aortic dissection in Turner syndrome. In all except 5, predisposing risk factors of coarctation, bicuspid aortic valve, and/or HBP were present. Of these 5, sufficient information regarding predisposing risk factors was provided for only 2. No phenotype:karyotype correlations could be drawn with any certainty.**

Conclusions. **When the diagnosis of Turner syndrome is made, a screening echocardiogram should be obtained. Referral to a cardiologist first may be appropriate, but physical examination does not substitute for visualization. Individuals with and without evidence of structural cardiac malformations should be monitored for HBP on a lifelong basis. In the absence of structural cardiac malformations or HBP, the risk for aortic dissection appears small, and repeated echocardiography or magnetic resonance imaging to follow aortic root diameters does not appear to be warranted based on data currently available. Protocols for following patients with structural malformations need to be individualized, and wholesale recommendations have little merit. A longitudinal study using magnetic resonance imaging or cardiac echocardiography to establish normal parameters for aortic root diameters and to follow aortic root changes is needed.** *Pediatrics* **1998;101(1). URL: http://www.pediatrics.org/cgi/content/full/101/1/e11;** ***aortic dissection, Turner syndrome, sex chromosome aneuploidy, hypertension, congenital heart disease, mortality.***

ABBREVIATIONS. Coarct, coarctation of the aorta; BAV, bicuspid aortic valve; MVP, mitral valve prolapse; HBP, hypertension; AS, aortic stenosis; ASD, atrial septal defect; MS, mitral stenosis; VSD, ventriculoseptal defect.

The occurrence of cardiac malformations in Turner syndrome (gonadal dysgenesis with sex chromosome aneuploidy) has long been recognized.[1] The most common heart defects are coarctation of the aorta (Coarct) and bicuspid aortic valve (BAV). A host of other structural alterations are also found.[2–4]

More recently, an increased risk for aortic dissection has been suggested,[5] a concern that has resulted in a recommendation for repeated (annual) echocardiography[6] that, in turn, has generated a heated debate.[7–11]

I report here the cardiac findings in a cohort of individuals with Turner syndrome that has been followed in a clinic established in 1977[12,13] to delineate the natural history of Turner syndrome. I review the literature and make recommendations for care and additional investigation based on these data.

MATERIALS AND METHODS

A total of 244 of 462 individuals with karyotype-proven Turner syndrome in our clinic population have had cardiac echocardiography performed on at least one occasion. An additional 28 have had normal examinations by cardiologists, but they are not included in the results, because structural malformations may not result in detectable murmurs or electrocardiography changes. Of the remaining 190 patients, 11 were detected prenatally and the pregnancies terminated. The remainder have been lost to follow-up or refused evaluation by cardiologists and/or echocardiography.

Participants have been recruited from a variety of sources. No systematic approach to cardiologists or cardiac clinics has been

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Received for publication Jun 17, 1997; accepted Aug 4, 1997.

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made. Only those patients with hypoplastic left heart syndrome were first referred for cardiac disease. Patients have been referred primarily for diagnostic evaluation (because of congenital lymphedema, dysmorphic features, short stature, or primary amenorrhea) and for genetic counseling and management after the diagnosis was made either prenatally or postnatally. Referral sources have included pediatricians, family practice physicians, medical geneticists, dermatologists, perinatologists, internists, gynecologists, endocrinologists, orthopedists, lay support groups, and self-referral.

Among these 244 individuals, the average follow-up time from diagnosis of Turner syndrome to date of last contact was 10 years; for many, all medical records were available including those predating the karyotypic confirmation of diagnosis. The number of visits for each patient ranged from 1 to 43, with a mean of 10.

The echocardiography has been performed at a variety of institutions. The majority were done at Children's Hospital and Medical Center, Seattle, WA.

Literature review included searching Medline from 1965 to the present and reviewing earlier citations in the bibliographies of later case reports.

RESULTS

Of 244 individuals, 136 had cardiac abnormalities, including structural malformations, hypertension (HBP), conduction defects, and mitral valve prolapse (MVP). Details are given in Table 1 and compared with those found in another large series in the recent medical literature.[3] The distribution of cardiac malformations by karyotype in this clinic population and from studies in the literature[3,14–18] is detailed in Table 2.

The mean age at the time of their last evaluation or contact with us of the entire clinic population is 18.4 years (range, 0 to 80; SD, 13.7 years). The mean age of those with cardiac findings, including HBP alone and MVP is 21.1 years (range, 0 to 80; SD, 16 years). Those without cardiac abnormalities have a mean age of 15.0 years (range, 0 to 76.6; SD, 12.7). Because HBP is a finding more common among the older patients, these differences are not surprising.

TABLE 1. Cardiac Findings in Turner Syndrome

	This Study	Gøtzsche et al[3]
Total number of patients	462	393
Echocardiography performed	244	179
	n (%)	n (%)
Structural abnormalities	96 (40)	46 (26)
Coarctation only	23 (9)	14 (8)
Bicuspid valve only	24 (10)	21 (12)
Both	4 (2)	4 (2)
Coarctation and other structural*	7 (3)	0 (0)
Aortic stenosis/regurgitation	11 (5)	5 (3)
Pulmonic valve	2 (1)	2 (1)
Other structural†	25 (10)	0 (0)
Nonstructural abnormalities	40 (16)	Not indicated
HBP	30 (12)	
Conduction defects	3 (1)	
MVP	6 (2)	
Pericardial effusion	1 (0.4)	

* Includes coarct/ASD (1); coarct/AS/partial anomalous pulmonary venous return (1); coarct/BAV/MS (1); coarct/left bundle branch block (1); coarct/BAV/ventriculoseptal defect [VSD] (1); coarct/BAV/AS/VSD (1); coarct/AS (1).

† Includes hypoplastic left heart (3); ASD (4); VSD (1); ASD/VSD (1); ASD/VSD/patent ductus arteriosus (1); ASD/cleft mitral valve (1); ASD/MR (1); TR/MR (2); TR (2); scimitar syndrome (1); sinus venosus (1); pulmonary artery kinking (1); BAV/AS/AI/pulmonary artery stenosis (1); MR (1); PDA (1); cleft mitral valve/ostium primum (1); AI/MR (1); BAV/AS (1).

Of 24 patients with BAV alone, 14 had had auscultatory evaluation by a cardiologist on one or more occasions before echocardiography. Of these (Table 3), 12 had no detectable murmur.

Causes of death in this clinic population are detailed in Table 4. Four neonatal deaths were attributable to cardiac causes. One patient died at 22.5 years of end-stage cardiac failure attributable to cleft mitral valve. Three other adults died of presumed or confirmed cardiac causes; details are given in Table 4.

In addition to the two individuals who died with or because of aortic dissection, one child has had ballooning of the aorta occur at the site of a coarctation repair. She continues to do well.

In the literature, there have been 42 instances of aortic dissection occurring in individuals with a clinical diagnosis of Turner syndrome and one with dilatation of the aorta and aortic regurgitation only[2,5,19–51] (Table 5). For 12, no karyotype information was given[19–22,32,34,43–45]; 4 had only buccal smears obtained.[26–28,33] Three had had karyotyping performed, but specific results were not given.[39,50] Twenty-nine of the 42 had preexisting Coarct, BAV, or both. Three of these 29 patients experienced dissections immediately after coarctation repairs.[36] One individual had aortic regurgitation and left ventricular hypertrophy noted before dissection, without other structural abnormalities.[25] One patient had aortic regurgitation[31] and another had aortic stenosis[50] without coarctation or BAV. Sixteen individuals had HBP of whom 5 were not known to have structural cardiac malformations[19,34,38,42,51]. Only five individuals had no known predisposing risk factors for aortic dissection.[25,39,41,46] Of these, one did not have an echocardiogram performed,[25] no information about the aortic valve was given for a second,[25] and no information about coarctation or bicuspid valve was given for a third.[39]

Of 45 individuals from the medical literature and this clinic population, only 3 experienced dissection of the aorta in the absence of documented predisposing risk factors.

DISCUSSION

There are three questions that need to be answered about management of the cardiac aspects of health care for individuals with Turner syndrome: 1) What is the risk for cardiac complications in this population? 2) What is an appropriate program for management including screening and monitoring? 3) What studies need to be performed to better answer questions 1 and 2?

Risk

Malformations

The increased risk for congenital heart malformations in Turner syndrome is undisputed, with a prevalence ranging from 17% to 45%[1,3,14–18] (this study). Although there are differences among surveys as to the prevalence of specific lesions, eg, coarctation versus BAV, these differences are unimportant from a patient-management standpoint. The different over-

TABLE 2. Cardiac Malformations by Karyotype

Karyotype	This Study*	Gøtzsche et al[3]	Mazzanti et al[14]	Hou et al[15]	Parchment et al[16]†	Moore et al[17]	Gianzo et al[18]	Total
45,X	59/131 (45)	39/103 (38)	6/27 (22)	7/26 (27)	2/14 (14)	8/12 (67)	3/6 (50)	124/318 (39)
45X/46,XX	9/27 (33)	1/14 (7)	1/5 (20)	4/15 (27)	—	1/7 (14)	1/2 (50)	17/20 (24)
46,X,i(Xq)	3/13 (23)	0/7 (0)	0/5 (0)	0/2 (0)	—	—	—	3/27 (11)
45,X/46,X,i(Xq)	3/17 (12)	2/13 (15)	0/7 (0)	0/3 (0)	—	—	0/2 (0)	5/42 (12)
45,X/46,X,+r(X)	7/18 (39)	1/13 (7)	2/5 (40)	—	1/3 (33)	0/1 (0)	—	11/40 (28)
45,X/46,X,+ mar	0/3 (0)	0/3 (0)	—	—	—	—	—	0/6 (0)
45,X/46,XY	8/14 (57)	1/3 (33)	—	0/2 (0)	2/2 (100)	—	0/2 (0)	11/23 (48)
45,X/46,X,abn Y	0/1 (0)	1/1 (100)	—	—	—	—	—	1/2 (50)
Other‡	7/22 (32)	1/22 (5)	0/6 (0)	0/1 (0)	2/4 (50)	—	1/7 (14)	11/62 (18)
Total	96/244 (39)	46/179 (26)	9/55 (17)	11/49 (22)	7/23 (30)	9/20 (45)	5/19 (26)	183/589 (30)

* Does not include conduction defects, MVP, pericardial effusion, pulmonary artery kinking.
† A total of 63 individuals were evaluated. Karyotypes were only given for those groups in which malformations were found.
‡ For example, 45,X/47,XXX; 45,X/46,XX/47,XXX; 45,X/47,i(Xq), i(Xq); 45,X/46,X + complex rea(X).
Number of affected individuals over the number of individuals evaluated with the same chromosome complement. Percentages are given in parentheses.

TABLE 3. BAV and Murmur

Age at Examination	Presence/Absence Murmur
7 Weeks	−
9 Months	−
2 Years	−
2 1/12 Years	−
3 3/12 Years	−
5	+
6	+
10	−
12	−
Birth/12 years/13 years	−/−/+
15	−
12/19	−/+
24	−
40	−

Individuals with BAV detected by echocardiography in whom auscultory evaluation by cardiologist was performed before to echo.

all rates and distribution of specific lesions may simply be attributable to the small number of subjects in most studies.

The most common lesions are Coarct, BAV, or both, followed by other aortic valve abnormalities. Hypoplastic left heart occurred in three of the patients with Turner syndrome in this clinic and has been reported in others.[52] It is a rare malformation and affects males more commonly. Its presence in a female newborn is an indication for karyotyping.

There are, in my opinion, inadequate data to allow for conclusions regarding phenotype:karyotype correlations in regard to congenital cardiac malformations in Turner syndrome. The number of individuals with the less common karyotype groups that have been studied is simply too small to analyze in a meaningful way. It appears that the occurrence of cardiac malformations among patients with an isochromosome Xq, with or without mosaicism for a 45,X cell line, is lower than for the 45,X patients and the Turner syndrome population as a whole (8/69, 12% vs 124/318, 39%, and 181/519, 35% [all except those with iXq]). Whether this difference is real ($\chi^2 = 20.64$; $P = .0003$) or an artifact because of the small number of patients, the absolute risk for cardiac involvement in patients with i(Xq) is high enough to warrant a similar program of monitoring.

Aortic Dissection

It is well established that Coarct, BAV, and HBP are associated with a risk for aortic dissection in populations without Turner syndrome.[53] Hirst et al,[54] in a report on their patients and a review of the literature, found coarctation in 9% to 23%, BAV in 23% to 42%, and HBP in 63% of cases of aortic dissection. Gore and Seiwert[55] reviewed 85 cases of dissection of the aorta. Of these, 8 had BAV, 3 had coarctation, 1 had both, 2 had BAV and another cardiac abnormality, 1 had coarctation and arachnodactyly. It is reasonable to assume that patients with these findings and Turner syndrome are at no less risk than individuals with these features without Turner syndrome. There is little evidence to suggest their risk is higher.

There have been two studies suggesting that baseline aortic root diameters in Turner syndrome are increased.[56,57] Allen and colleagues[56] evaluated 28 girls with Turner syndrome by echocardiography and compared their aortic root diameters with those of a control group of girls with similar body surface area measurements. The mean age of the latter group was 4.7 years younger. An age-matched control group was not evaluated. Although the mean aortic root diameter of the patients with Turner syndrome was significantly greater than that of the control group (2.59 ± 0.26 cm and 2.24 ± 0.25 cm, respectively, $P = <.001$), nonetheless, the aortic root diameters of the patients with Turner syndrome were still well within normal limits. Dawson-Falk and colleagues[57] evaluated 40 patients with Turner syndrome by echocardiography and MRI. Aortic root diameters for all were within the normal range for body surface area, although, again, the mean aortic root diameter of the group was above the mean for a normal population matched for body surface area.

It is not inherently obvious that the appropriate control group for these patients is one matched for height rather than for age. It is unproven that aortic root diameters that are relatively large for body surface area, yet still well within normal limits, imply a risk for progressive dilatation.

TABLE 4. Causes of Death in this Study Population

Age	Karyotype	Cause
Birth	45,X	Hypoplastic left heart
Birth	45,X/46,X, + r(X)	Hypoplastic aortic valve leaflet, persistent fetal circulation, meconium aspiration, cerebral edema
Birth	45,X/46,X,i(Xq)	Hypoplastic left heart
Birth	45,X	Multicystic kidneys
Birth	45,X	Osteogenesis imperfecta
Birth	45,X	Hypoplastic left heart
5 Months	45,X	SIDS, hypoglycemia
5 Months	45,X	SIDS
2.9 Years	45,X	Apnea
6.4 Years	45,X/46,X,i(Xq)	Wasting muscle disease, increased intracranial pressure (unknown cause)
7.9 Years	45,X/45,XX, monosomy G	Unknown, severe developmental delay
19.5 Years	46,X,i(Xq)	Car accident
22.5 Years	45,X/46,X, $+r^1$/46,X, $+r^2$/47,X,$+r^1$,$+r^2$	Congestive heart failure, cleft mitral valve
23 Years	45,X	River rafting accident
27 Years	45,X	Malignant hyperthermia
33 Years	46,X,Xp^-	Unknown
38.9 Years	45,X	Found dead in bed. Traumatic dissection aortic attributable to blunt chest trauma 3 years earlier. Presumed diagnosis rupture of stable dissection, but cardiologist believed attributable to arrhythmia because patient had no prodromal symptoms before death. No autopsy. Also had essential HBP.
39.6 Years	45,X	Autopsy, aortic dissection from common carotid to diaphragm. No structural cardiac abnormalities. Patient had malignant obesity (146 cm height/145 kg weight), with a 22 year history of HBP
44.8 Years	45,X	Automobile accident
45 Years	45,X/46,X,+r(X)	Presented to emergency room (ER) with hypotension and chest pain. Ultimately died of cardiac arrest. ER diagnosis was myocardial infarction. Reviewed with ER physician possibility of dissection; believes signs and symptoms consistent with myocardial infarction, not dissection. No autopsy. Patient had severe diabetes and HBP. No echocardiogram ever performed.
51.5 Years	45,X	Cervical myelopathy, acute febrile syndrome
79.9 Years	45,X	Arteriosclerotic heart disease; congestive heart failure
80.2 Years	45,X/46,X, i(Xq)/47,X,i(Xq), i(Xq)	Old age

To date, no longitudinal studies of aortic root diameter changes in patients with Turner syndrome have been performed. There is no evidence to suggest that patients with Turner syndrome experience progressive dilatation of the aorta over time, in the absence of predisposing risk factors, as occurs in Marfan syndrome, and no evidence to support recommendation for prophylactic use of β blockers. The risk for aortic dissection in Turner syndrome appears to be almost entirely a consequence of structural cardiac malformations and hemodynamic risk factors, rather than a reflection of an inherent abnormality in connective tissue. In those individuals with structural changes known to predispose to dissection, it is not known whether dissection is an acute process or the result of slow, progressive dilatation.

HBP

HBP is found in these patients more commonly than in the general population. Thirty of my patients have or have had HBP without structural cardiac malformations. Age at onset in most has been in the 20's and 30's, although 4 patients developed essential HBP before adulthood. Four of the 30 have elevated lipids and a positive family history for the same. Hypothyroidism and variations in ovarian hormone supplementation may also play a role in the risk for HBP and hyperlipidemia. This population has not been evaluated systematically for hyperlipidemia, and I cannot make any inferences regarding lipid metabolism and attendant cardiac risks in Turner syndrome.

Management

Baseline echocardiography is absolutely indicated when the diagnosis of Turner syndrome is made in an individual. Dependence on ausculatory findings is inadequate, as demonstrated in this study (Table 3). With a baseline risk for cardiac malformations approaching 40%, the yield of echocardiography is sufficiently high to warrant its wholesale use in these patients. If cardiac malformations are detected, recommendations for additional monitoring need to be individualized, and until we have shown differently, probably ought to be similar to recommendations for the specific cardiac lesion any individual (eg, antibiotic prophylaxis in the presence of BAV, repeat evaluation and echocardiography in subclinical Coarct). All patients should be followed with age-appropriate examinations during early childhood and thereafter by yearly physical examination with checking of blood pressure and thyroid function. The detection of abnormalities at any age will require individually tailored plans for management. Monitoring lipids is probably reasonable to perform in patients with Turner syndrome but should remain at the discretion of the health care provider until a clear risk for lipid-related disease in these patients is established.

TABLE 5. Case Reports of Aortic Dissection in Individuals With Turner Syndrome

Citation	Age (years)	Karyotype	Coarctation/BAV	Other Preexisting Risk Factors	Site of Dissection	Histology	Death
2	30	45,X	−/+	HBP × 10 years	Aortic sinus	Myxomatous change in valve	−
5	27	45,X	−/+		Asc	Long-term changes	+
5	19	45,X	+(Repairs age 2/9)/+ replaced				
19	27	NI	−/−	HBP × 4 years	Asc	CMN	−
20*	23	NI	+/NI		Desc		−
21*	10	NI	+(Repair age 5)/+		Asc	CMN	+ (Age 14)
21*	16	NI	+ (Repair age 8), repair of recurrent stenosis with patch age 9/NI		Site of patch		+
22	25	NI	−/+		Asc		−
23	19	45,X	+/+, AS, AR		Asc		−
24	37	45,X	−/+, AS, AR	Acute SBE, HBP × 23 yrs	Asc/Desc	Myxomatous change valve–CMN	+
25	39	45,X	−/NI	−	Asc/Desc	Puckering of intima at level of ductus	+
25	38	45,X	−/AR	LVH	Dilat Asc	Autopsy refused	+
25	30	45,X/46,X +ring	No echo	−		CMN	+
26	40	Buccal	−/+, AS	LVH, angina	Asc/thoracic	CMN	+
27	15	Buccal postmortem	+/+	HBP × 3 years	Asc	CMN	+
28	19	Buccal	+/+	HBP	Asc	CMN	−
29	37	45,X	? Hypoplasia Desc/Asc aorta/+, AI, AS	LVH Rheumatic fever, age 27	Trans/Desc	CMN	+
30	34	45,X	+/−	Stenosis renal arteries HBP (recent) Incomplete RBBB × 16 years	Desc		−
31	28	45,X	−/−, AR		Asc	Aortic diameter increase over 12 years Myxomatous changes valve	−
32	27	NI	−/+		Asc	CMN	
33	34	Buccal	+/+	HBP × 20 years	Desc	Atherosclerosis	+
34	4	NI	+/NI	HBP × 2 years	Asc	CMN	+
34	20	NI	−/NI	Mild HBP	Asc	CMN	+
35	8	45,X	+ (Subclinical) Kink/+	Tachycardia, RVH	Arch	Adventitial fibrosis/− CMN	
36	12	45,X	+/NI	Immediately after surgery for coarct	Site of Repair	No abnormal pathology	+
36	8	45,X	+/NI	Immediately after surgery for coarct	Site of repair	No abnormal pathology	−
36	9	45,X	+/NI	Immediately after surgery for coarct	Site of repair	No abnormal pathology	−
37	NI	45,X	+/−	NI	Desc		+
38	64	45,X/46,XY	−/NI	HBP	Asc/Desc	Medical treatment, no surgery	−
39*	36	"Mosaic"	NI/NI	−	NI	NI	+
40	18	45,X	−/−	−	Dilatation of Asc aorta with AR, no dissection	−	−
41	19	45,X	−/−	−	Asc	CMN	−
42	34	45,X	NI/NI	Mild HBP	NI	NI	NI
43*	27	NI	+/NI	AR	Aortic ring	NI	NI
44	43	NI	−/+	Labile HBP, PAT, Simple coronary ostium	Asc/Desc	NI	−
45	45	NI	+/−	Coarct repair Aortic valvostomy Severe aortic stenosis	Site of repair	NI	−
46	27	NI	−/−	−	Abdominal renal arteries to bifurcation	−	−
47	36	45,X	−/+, AS	−	Asc	−	−
48	25	45,X	+/−	−	Asc	CMN	+
49	48	45,X	−/+	HBP	Asc/Desc	CMN	+

TABLE 5. Continued

Citation	Age (years)	Karyotype	Coarctation/BAV	Other Preexisting Risk Factors	Site of Dissection	Histology	Death
50	15.5	"Consistent with Turner syndrome"	+/−, AS repaired	−			+
50	19	"Consistent with Turner syndrome"	−/−, AS	HBP	Asc/Desc	CMN	+
51	42	45,X	−/−	HBP × 10 years RBBB	Desc	CMN	−
This study	39.5	45,X	−/−	HBP × 25 years Cardiomegaly	Desc	−	+
	39	45,X	−/−	HBP Traumatic dissection, blunt chest trauma	Trans/Desc	−	+
	9.5	45,X	−/−	S/P cardiac repair	At repair site	−	−

* In Japanese; abstract in English only. NI indicates No information; CMN, cystic medionecrosis; ASC, ascending aorta; DESC, descending aorta; HBP, high blood pressure; BAV, bicuspid aortic valve; AS, aortic stenosis; AR, aortic regurgitation; LVH, left ventricular hypertrophy; SBE, subacute bacterial endocarditis; RBBB, right bundle branch block.

Research

To determine whether a risk for dissection of the aorta higher than that in the general population with similar risk factors exists in Turner syndrome, and whether the occurrence of dissection is preceded by slow dilatation of the aortic root, perhaps allowing for prophylactic intervention, a longitudinal study using repeated echocardiography needs to be performed. Is there an acceptable range of aortic root diameters in this population that is different from that of the normal population? Comparisons with age-matched controls and height-matched controls, both from the general population (eg, short women without sex chromosome abnormalities) and those with other skeletal dysplasias (normal aortic root diameters may be different for population groups that are generically small, such as children, rather than those that are skeletally small only), should be done. This may allow us to identify a subset of individuals with Turner syndrome whose aortic root diameters fall outside the range for Turner syndrome and to determine whether they are at higher risk for aortic dissection and therefore should be followed more closely.

A systematic longitudinal and cross-sectional evaluation of blood pressure and lipids, correlated with family history, diet, weight, ovarian hormone replacement, and thyroid functions needs to be performed. Reliance on data from individual patients results in unacceptable bias. Individuals with signs and symptoms are more likely to be tested; such information is primarily cross-sectional, and not longitudinal, and often unsuitable for interpretation, because not all of the possible confounding factors, such as family history, have been evaluated.

It is difficult to design, fund, and perform the longitudinal natural history studies that are necessary to better answer the questions of risk and management. These studies require long-term commitment on the part of both the investigator and the subject, both of whom are at risk for burnout, relocation, or death. These studies require consistency among collaborators. Laboratories differ in their methods and standards, and echocardiographers vary in their skill and interpretation. Funding is an issue. Although some of these tests are warranted on a health care basis and therefore justifiably charged to insurance, others can only be viewed as potentially useful to the Turner syndrome population as a whole, and not necessarily indicated for the given individual.

Until we find the means to perform these studies, however, we will continue to be frustrated in our ability to provide patients with Turner syndrome and the practitioners who care for them prudent, cost-effective, beneficial guidance.

ACKNOWLEDGMENTS

This work was supported in part by a grant from the Welch's Genesis Fund.

I thank Dr Nancy Hopwood for her input, Genentech for sharing references, Stan Vlcek and Dr Ephrat Levy-Lahad for translations of Czech and Hebrew, and Tracy Kicklighter for secretarial support. As always, I also thank the many physicians and genetic counselors for their referrals, and the patients and their families for their patience and persistence.

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DOI: 10.1542/peds.101.1.e11

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