Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome

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Abstract

The aim of the study was to establish the prevalence of cardiovascular malformations in females with Turner's syndrome and analyse possible associations with the various karyotypes. One hundred and seventy nine of 393 females who had Turner's syndrome diagnosed in Denmark were examined. Complete chromosome analysis was available in all cases. Clinical examination, electrocardiography, and echocardiography including Doppler were performed.

The distribution of the various karyotypes was 45,X, 58%; mosaic monosomy X, 35%; and structural abnormalities of the X chromosome, 7%. In 46 (26%) of the females a total of 69 cardiovascular malformations were found; aortic valve abnormality (18%) and aortic coarctation (10%) being the most common. There was a significant difference in the prevalence of cardiovascular malformations between 45,X and mosaic monosomy X (38% *v* 11%), primarily due to a significant difference in the prevalence of aortic valve abnormalities and aortic coarctation. Pulmonary valve abnormalities were seen only in females with mosaic monosomy X but the prevalence was low (3%). No patient with structural abnormalities of the X chromosome had cardiovascular malformations.

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Turner's syndrome is a genetic abnormality in females and the karyotype can be monosomy X (45,X), mosaic monosomy X, or a structural abnormality of the X chromosome. The syndrome is characterised by short stature and gonadal dysgenesis, and is associated with a number of congenital abnormalities including cardiovascular malformations. In published series of Turner's syndrome the percentage of those with cardiovascular malformations has ranged from 17% to 47%; aortic coarctation and bicuspid aortic valve being the most common lesions.[1–3] However, these studies have all been relatively small hospital based series from departments of paediatrics, cardiology, or endocrinology. Due to possible selection bias, these data may not truly reflect the prevalence of cardiovascular malformations in Turner's syndrome.

An association of aortic valve disease and aortic coarctation with 45,X karyotype and pulmonary stenosis with mosaic monosomy X has previously been suggested,[4] but prevalence studies are not available.

Since 1963, all females with Turner's syndrome diagnosed in Denmark have been listed in the Danish National Cytogenetic Register. The presence of this register made it possible for us to examine a large and relatively unselected group of females with Turner's syndrome. The introduction of echocardiography with the application of Doppler techniques has made non-invasive detection of cardiovascular malformations possible, including identification of minor cardiac lesions that may otherwise remain asymptomatic for years. Doppler ultrasonographic modalities have not been used in previous studies of females with Turner's syndrome.

The purpose of our study was to establish the prevalence of cardiovascular malformations and investigate any possible associations between the various genotypes and cardiovascular malformations.

Patients and methods

In March 1988, 393 females with Turner's syndrome were registered in the Danish National Cytogenetic Register. We were able to obtain contact with 223 through direct contact, through the family doctor, or through the National Association of Turner Contact Groups, and 179 agreed to participate. The mean age of the females examined was 23 years (range 6 months to 46 years). Results from chromosome analysis were available in all.

In each case a history was taken concerning cardiovascular symptoms and former operations. Clinical examination, electrocardiography, and echocardiography were performed by a cardiologist blinded to the specific karyotype.

Echocardiography including Doppler studies was performed using a Toshiba 60 or 65A. Pulsed and continuous wave Doppler as well as colour flow mapping was performed with a 2·5 MHz transducer. The echocardiography included standard M mode measurements and two dimensional evaluation from all standard planes. Flow velocities across the aortic, mitral, pulmonary, and tricuspid valve as well as in the ascending and descending thoracic aorta were obtained using pulsed and continuous Doppler modalities.[5] All echocardiograms were recorded on videotape and later reviewed blindly by another cardiologist. The diagnosis of bicuspid aortic valve and mitral valve prolapse followed standard criteria.[2 6]

The χ^2 test with the Yates's correction and Fisher's exact test were used in comparison between the 45,X group and the mosiac monosomy X group; $p<0·05$ was considered significant.

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Table 1 Distribution of karyotypes in 179 females with Turner's syndrome

	Karyotypes	No	
Complete monosomy	45,X		103
Mosaic monosomy X			63
	45,X/46,XX	14	
	45,X/46,X,r(X)	13	
	45,X/46,X,i(Xq)	13	
	45,X/46,XY	3	
	45,X/46,X+mar	3	
	45,X/47,XXX	3	
	45,X/46,X,dic(Xq)	3	
	45,X/46,X,i(Xq)/47,X,i(Xq),i(Xq)	3	
	45,X/46,X,del(X)(p11)	2	
	45,X/46,X,del(X)(q11)	1	
	45,X/46,X,i(Yp)	1	
	45,X/46,X,dic(X;X)(p22;p22)	1	
	45,X/46,Xinv(X)(p22;q24)	1	
	45,X/46,X,i(Xq)/46,X,r(X)	1	
	46,XX/46,X,i(Xq)	1	
X structural abnormalities			13
	46,XX,i(Xq)	7	
	46,X,del(X)(p11)	2	
	46,X,del(X)(q25)	1	
	46,X,del(X)(q13)	1	
	46,X,+mar	1	
	46,X,dic(X;X)(p21;p21)	1	

The study was approved by the local ethical committee for medical science.

Results

Of the 179 subjects examined 103 (58%) had complete monosomy X, 63 (35%) had mosaic monosomy X, and 13 (7%) had a structural X chromosome abnormality (table 1). In 46 (26%) females a total of 69 cardiovascular malformations were found (table 2). Aortic valve abnormalities were seen in 33 (18%), the valve being bicuspid and/or stenosed and/or regurgitant. Bicuspid aortic valve was the most common malformation being detected in 25 (14%). Eight of the bicuspid valves were either stenotic and/or incompetent. Of eight females with aortic stenosis four had a bicuspid aortic valve, and of the 11 with aortic regurgitation four had a trileaflet aortic valve with no morphological abnormality detected on two dimensional evaluation. Aortic coarctation was found in 18 (10%), all located in the typical position in the descending thoracic aorta.

Among subjects with 45,X karyotype 39 (38%) had cardiovascular malformations, while this was found in only seven (11%) with mosaic monosomy X ($p<0{\cdot}001$). No cardiovascular malformations were found in the small group with a structural X chromosome abnormality. The association between the cardiovascular malformations and karyotypes is shown in table 3. In subjects with 45,X, aortic coarctation was more prevalent than in mosaic monosomy X: 17% *v* 2% ($p<0{\cdot}01$). Aortic valve abnormalities were seen in 29 (28%) females with 45, X, but only in four (7%) with mosaic monosomy X ($p<0{\cdot}001$). Ten (10%) subjects had malformations in more than one cardiovascular site and all had the 45,X karyotype ($p<0{\cdot}05$).

Table 2 Cardiovascular malformations in 46 females with Turner's syndrome

Patient No	Age (years)	Karyotype	Type of cardiovascular malformation				
			Aortic coarctation	Bicuspid aortic valves	Aortic stenosis	Aortic regurgitation	Other
1	24	45,X	+			+	
2	31	45,X		+			
3	23	45,X	+		+	+	
4	39	45,X				+	
5	16	45,X	+				
6	19	45,X	+	+			
7	11	45,X	+				
8	6	45,X		+			
9	9	45,X	+				Mitral regurgitation
10	35	45,X		+		+	
11	22	45,X	+				
12	8	45,X	+	+			PDA
13	5	45,X		+	+		
14	32	45,X	+			+	
15	24	45,X		+			
16	46	45,X			+		
17	16	45,X		+	+	+	
18	21	45,X		+			
19	37	45,X		+			
20	15	45,X		+			Dextrocardia
21	26	45,X	+	+			
22	25	45,X		+			
23	31	45,X		+			
24	30	45,X	+				
25	14	45,X		+			
26	39	45,X	+				
27	11	45,X	+				
28	22	45,X	+				
29	24	45,X		+			
30	8	45,X			+		
31	4	45,X	+				PDA, PAPVD
32	18	45,X	+	+		+	
33	25	45,X		+		+	
34	17	45,X		+			
35	16	45,X				+	
36	22	45,X	+				
37	3	45,X			+	+	
38	29	45,X		+		+	
39	20	45,X		+			
40	44	45,X/46XY		+	+		
41	19	45,X/46XX	+				
42	22	45,X/46,Xi(Xq)		+			
43	10	45,X/46,Xr(X)					Pulmonary stenosis
44	42	45,X/46,Xi(Xq)		+	+		
45	17	45,X/46,Xi(Yp)					Pulmonary regurgitation
46	7	45,X/46,Xi(Xq)/47,Xi(Xq)		+			

PAPVD=partial abnormal pulmonary venous drainage, PDA=persistent ductus arteriosus.

Table 3 Number (%) of females with cardiovascular malformations in the different karyotypes of Turner's syndrome

Cardiovascular malformations	*Karyotypes*	
	45,X (n=103)	*Mosaic monosomy X (n=63)*
Aortic valve abnormality	21 (20)	4 (6)
Coarctation	8 (8)	1 (2)
Coarctation+aortic valve abnormality	6 (6)	0
Coarctation+OCM	3 (3)	0
Aortic valve abnormality+OCM	1 (1)	0
Pulmonary valve abnormality	0	2 (3)
Total	39 (38)	7 (7)

OCM=other cardiovascular malformations.
No females with structural abnormalities of the X chromosome (n=13) had cardiovascular malformations.

In six females, aortic coarctation as well as aortic valve abnormality was present. One female had aortic coarctation and mitral regurgitation due to a deformity of the mitral valve, one had a bicuspid valve and dextrocardia, one had aortic coarctation with a bicuspid aortic valve and persistent ductus arteriosus, and one had aortic coarctation, persistent ductus arteriosus, and partial anomalous pulmonary venous drainage. Isolated pulmonary valve stenosis was seen in one female and isolated pulmonary regurgitation in another, both with a mosaic monosomy X.

Twelve of the 18 with aortic coarctation had previously undergone surgery. In the remaining six the gradient across the coarctation ranged from 16 to 50 mm Hg (mean 31 mm Hg). Of the eight females with aortic stenosis three had received surgery and one had had balloon dilatation with no restenosis or aortic regurgitation, while the remaining four had peak gradients ranging from 20 to 64 mm Hg (mean 35 mm Hg). The girl with pulmonary stenosis had had a successful balloon dilatation.

Discussion

Turner's syndrome is associated with a substantial increase in the prevalence of cardiovascular malformations. Reported prevalence rates have varied from 17% to 47%.[1-3] This considerable variation probably reflects problems in selection criteria in hospital series and the small sample sizes.

In our study, which is the largest reported, we found that 26% had cardiovascular malformations. Females examined included 179 of 393 patients who had Turner's syndrome diagnosed in Denmark, and the distribution of karyotypes in the study is similar to other studies of the genotype distribution.[7 8] It is furthermore a population based study, the karyotype as registered in a central karyotype register being the inclusion criterion. Accordingly, we have no reason to believe that the prevalence of cardiovascular malformations should be significantly different in those who did not participate in the study.

From a large study of sex chromosome abnormalities in liveborn children we know that the incidence rate of Turner's syndrome at birth in Denmark is approximately one in 2000 girls.[9] Even though the Danish National Cytogenetic Register includes all patients with diagnosed Turner's syndrome we can estimate that females enlisted represent only approximately 35% of the total population with Turner's syndrome, the rest remaining undiagnosed. In the major subgroup of females with undiagnosed Turner's syndrome it seems reasonable to expect a somewhat lower prevalence of cardiovascular malformations as clinical signs or symptoms have not resulted in karyotype examination. On the other hand children with Turner's syndrome and cardiovascular malformations may die in utero or in the neonatal period, for example, patients with severe aortic coarctation.

Bicuspid aortic valve is thought to be the most common cardiovascular malformation in the general population occurring in 1% to 2%.[10] In previous echocardiographic studies the prevalence of bicuspid aortic valve in Turner's syndrome has ranged from 9% to 34%.[2 3 11] We found bicuspid aortic valves in 14%. Adding females with aortic stenosis and/or regurgitation without a bicuspid valve a total of 18% had abnormal aortic valves. It is generally agreed that a bicuspid aortic valve predisposes to valvular stenosis and/or insufficiency with advancing age,[12] and indeed 32% of those with bicuspid aortic valve had either stenosis or insufficiency of the valve. Apart from the haemodynamic consequence of an abnormal valve, susceptibility to infective endocarditis warrants antibiotic prophylactic treatment.

The prevalence of aortic coarctation has varied in previous studies from 2% to 19%.[1-3] We found 10% with aortic coarctation. In the Danish population in general the prevalence is 0·042%.[13] The prevalence of mitral valve prolapse in healthy young women is assumed to be 1% to 2%.[14] An extremely high occurrence of mitral valve prolapse in Turner's syndrome has been found in one study,[3] but using a standard definition we were not able to find any subject with this malformation.

Even though two studies have suggested an increased prevalence of cardiovascular malformations in females with 45,X compared with females with Turner's syndrome and other genotypes[1 4] a detailed analysis of prevalence has never been reported. Nora *et al* examined 36 females with Turner's syndrome and known cardiovascular disease and found an association between mosaic monosomy X and pulmonary stenosis, and between 45,X and aortic coarctation.[4] No abnormalities of the aortic valve were found in their study from the pre-echocardiographic era. In our study, the prevalence of cardiovascular malformations was significantly higher in 45,X karyotype (38%) than in mosaic monosomy X (11%). No subject with structural abnormalities of the X chromosome had cardiovascular malformations. Looking into the specific cardiovascular malformations a significantly higher prevalence of aortic coarctation and aortic valve abnormality was found in the 45,X group, and the combination of aortic coarctation and aortic valve abnormality was only seen in subjects with this karyotype. In contrast, two females with pulmonary valve disease both had mosaic monosomy X, suggesting an association between pulmonary valve disease and mosaic monosomy X, but the prevalence is low.

In a selected group of females with Turner's syndrome, Price *et al* found a reduction in life expectancy, particularly because of death due to cardiovascular malformations.[15] Furthermore, a few young women with Turner's syndrome and no evidence of cardiovascular disease who died from dissection of the aorta have been reported.[16] This may indicate an association between Turner's syndrome and weakness of the aortic wall. We conclude that Turner's syndrome is associated with a substantial increase in the prevalence of cardiovascular malformations primarily related to the 45,X karyotype. Aortic valve disease and aortic coarctation are the most common malformations and they are significantly more frequent in 45,X karyotype. Because of the therapeutic and prophylactic implications we recommend a cardiological examination including Doppler echocardiography in all females with Turner's syndrome, once the diagnosis is established.

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