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Cardiovascular Anomalies in Children and Young Adults with Ullrich-Turner Syndrome—The Erlangen Experience

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Summary

Background: Females with Ullrich-Turner syndrome (UTS) have typical clinical features such as short stature, ovarian failure, visible dysmorphic stigmata, and abnormalities in different organs such as kidney or heart.

Hypothesis: The aim of the present study was to analyze the distribution, prevalence, and relative risk of cardiovascular anomalies (CVA) in females with Ullrich-Turner syndrome (UTS) seen at one single center compared with that of the regional Bavarian population.

Methods: The associations between CVA and karyotype were determined. In all, 117 girls and women with UTS, aged between 3 and 43 years (median 17.4 years) were studied retrospectively. The detailed cardiologic status including echocardiography was available in all patients. The prevalences of each cardiovascular anomaly were determined. On the basis of published epidemiologic data of CVA in Bavarian children, we assessed the relative risks of each CVA.

Results: Thirty-five (29.9%) girls with UTS had at least one CVA. In all of these CVAs, coarctation of the aorta and bicuspid aortic valve occurred most often (18.5% each). The aortic malformations represented over two-thirds of all CVA (72.8%), whereas anomalies of the septum (8.6%), mitral valve (6.2%), pulmonary veins (4.9%), and other locations together accounted for the other third. Bicuspid aortic valve and partial anomalous pulmonary venous drainage were associated with the highest relative risk (RR) (3,603 and 1,293, respectively) compared with the Bavarian population. The overall RR of CVA was 48.7. Of the 117 girls and women examined, 64 (54.7%) had complete monosomy 45 X.

Conclusions: Our data demonstrate that about every third female with UTS is affected with at least one CVA, mainly left sided and associated with aortic structures. Our results underline the necessity of thorough cardiologic evaluation.

Key words: Ullrich-Turner syndrome, congenital heart disease, cardiovascular anomalies

Introduction

Females with Ullrich-Turner syndrome (UTS) have typical clinical features such as short stature, ovarian failure, visible dysmorphic stigmata, and abnormalities in different organs such as kidney or heart. Cardiovascular anomalies, in particular bicuspid aortic valve and aortic coarctation, were found to be very common in these girls and women, ranging from 17 to 47%.[1–3]

In recent years, most medical attention has been focused on the improvement of final height by recombinant human growth hormone therapy.[4–7] Another important therapeutic goal is substitution with estrogens in order to induce and maintain normal sexual development and to achieve optimal skeletal maturation. Thus, health surveillance in children with UTS was primarily conducted by pediatric endocrinologists. However, because of cardiovascular problems in infants and children with UTS, and the knowledge that reduced life expectancy in adult women with UTS is largely caused by cardiovascular disease, it became quite clear that a close cooperation with a cardiologist is inevitable for optimal care of these patients.[8]

The aim of the present study was to analyze the distribution and prevalence of cardiovascular anomalies (CVA) in patients with UTS seen at a single center. To estimate the population-based relative risks (RR) we compared the CVA prevalences of our UTS cohort with reported epidemiologic data of the same population. In addition, we correlated our results with the corresponding karyotype for evaluation of possible associations between CVA and genotype.

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Methods

Subjects

In all, 117 girls and women with UTS, aged between 3 and 43 years (median 17.4 years), who attended our endocrine and cardiologic outpatient department between 1980 and 2003, were studied retrospectively.

Data of echocardiographic investigation for evaluation of cardiovascular status were available in all patients. All cardiovascular anomalies had been diagnosed during infancy. All those (n = 18) with clinical and sonographic findings suggesting aortic coarctation (blood pressure difference between upper and lower limbs and/or increased pulsed-wave velocity in the descending aorta and/or a distinct narrowing of the upper descending aorta in two-dimensional echocardiography) underwent cardiac catheterization for confirmation. A tubular decreased diameter of the aorta distal to the left carotid artery was additionally defined as hypoplasia of the aortic arch. The diagnosis of aortic valve stenosis was made from typical sonographic findings, for example, a pulsed-wave velocity of > 2.0 m/s.

The life status (living or deceased) at the time of study was revealed. Chromosomal analysis in peripheral lymphocytes had been performed in all subjects. The exact karyotype, however, was available in 113 of 117 patients.

Data Analysis

The prevalence of each cardiovascular anomaly was calculated for the whole cohort. To assess population-based relative risks (RR), the prevalence of several CVA was compared with that in of Bavarian children.[9] The criteria of CVA assessment in this study was similar to ours and also included bicuspid aortic valves.

For statistical analysis the chi-square test was performed employing GraphPad Prism™ software, version 4.01 (GraphPad Software, Inc., San Diego, Calif., USA). Exact chi-square values for $p < 0.0001$ (two-sided) and confidence intervals (95%) are shown in Table I.

Results

Of all 117 subjects studied, 35 had at least one cardiovascular anomaly (CVA); this is equivalent to a prevalence of 29.9% in the study group. In these 35, we observed a total number of 81 single CVA. One or two single CVA were observed in 15 (42.9%) each; three CVA were found in three (8.6%); and four or more CVA were found in only two (5.7%) patients. Of 18 (55.6%) patients with coarctation of the aorta, 10 also had a bicuspid aortic valve, and 3 of these 10 also had aortic valvular stenosis. Of the 15 patients with bicuspid aortic valves, 6 also showed aortic valvular stenosis. Only two presented with an isolated bicuspid aortic valve.

Within the CVA group, coarctation of the aorta, all typically located juxtaductally, and bicuspid aortic valve occurred most often (18.5% each). The aortic malformations represented over two-thirds of all CVA (72.8%), whereas anomalies of the septum (8.6%), mitral valve (6.2%), pulmonary veins (4.9%), and other locations together accounted for the other third. Besides bicuspid valves and coarctation, valvular stenosis (12.3%), hypoplasia of the aortic arch (9.9%), regurgitation (2.5%), and dilatation of the ascending aorta (2.5%) were mostly found within anomalies of the aorta including the aortic valve. Aortic aneurysms occurred in only two patients (2.5% of all CVA, prevalence 1.7%). For details see Table II and Figure I.

Among the other anomalies, ventricular septal defect (VSD) (6.2%) and partial anomalous pulmonary venous drainage (PAPVD, 4.9%) were most frequent. A detailed distribution of all cardiovascular malformations is shown in Table II.

Bicuspid aortic valve and PAPVD were associated with the highest RR, (3,603 and 1,293). Aortic coarctation including hypoplasia and atresia of the aortic arch and valvular aortic stenosis were seen about 400-fold (469 and 400, respectively)

TABLE I Relative risks (RR) of various cardiovascular anomalies (CVA) compared with Bavarian children

	Patients with UTS N = 117 Prevalence (%)	Population [a] N = 983697 Prevalence (%)	RR	CI (95%)	Chi-square ($p < 0.0001$)
Bicuspid aortic valve	12.8	0.0036	3603	2023–6418	35340
PAPVD	3.4	0.0026	1293	458.5–3649	3427
Aortic coarctation [b]	15.4	0.0328	469	302.1–726.6	7520
Valvular aortic stenosis	8.5	0.0213	400	218.0–735.4	3432
VSD	4.3	0.2292	18.6	7.898–44.00	6677
ASD II	1.7	0.0921	18.6	4.689–73.47	1796
CVA	29.9	0.6249	48.7	36.90–64.28	1589

[a] Modified from Ref. No. 9.

[b] Including hypoplasia of the aortic arch.

Abbreviations: CI = confidence interval, PAPVD = partial anomalous pulmonary venous drainage, ASD = atrial septal defect, VSD = ventricular septal defect, UTS = Ullrich-Turner syndrome.

TABLE II Distribution of single cardiovascular anomalies (CVA), frequencies within all CVA, and calculated prevalences within the studied cohort

	N	Frequency (%) [a]	Prevalence (%) [b]
Aorta			
Coarctation incl. atresia			
Juxtaductal (distal LSA)	15	18.5	12.8
Arcus (proximal LSA)	2	2.5	1.7
Atresia	1	1.2	0.9
Valvular stenosis	10	12.3	8.5
Aortic valve			
Bicuspid	15	18.5	12.8
Dysplasia	1	1.2	0.9
Regurgitation	2	2.5	1.7
Aneurysm			
Ascending aorta	1	1.2	0.9
Aorta thoracica	1	1.2	0.9
Hypoplasia of the aortic arch	8	9.9	6.8
Others			
Proximal LSA stenosis	1	1.2	0.9
Dilatation ascending aorta	2	2.5	1.7
Septum			
ASD II	2	2.5	1.7
VSD	5	6.2	4.3
Mitral valve			
Stenosis	2	2.5	1.7
Prolapse	2	2.5	1.7
Regurgitation	1	1.2	0.9
Pulmonary veins			
PAPVD	4	4.9	3.4
Others			
LSVC	1	1.2	0.9
A. lusoria	1	1.2	0.9
Monoostial origin of coronaries	1	1.2	0.9
Dysplasia of *V. portae*	1	1.2	0.9
Esophageal varices	2	2.5	1.7

[a] Within all CVA.

[b] Within girls with UTS.

Abbreviations: LSA = left subclavian artery, LSVC = left superior vena cava. Other abbreviations as in Table I.

compared with the normal population. In contrast, the RR of septal anomalies (VSD, atrial septal defect [ASD] II) was only moderately elevated (18.6 each). Overall, RR of CVA was 48.7 (see Table I).

Of the 117 girls and women examined, 64 (54.7%) had complete monosomy 45 X, whereas X-mosaic monosomies were found in 18 (15.4%) and X-structural abnormalities in 27 (23.1%). In four subjects (3.4%), a not qualified marker chromosome was identified. Unfortunately, the exact karyotype of the chromosome analysis performed in an outside hospital was not available in four patients. Thus far, only two of the initial cohort have died. Both suffered from aortic aneurysms and presented with monosomy 45 X. The diagnosis of dissection (or rupture) was confirmed at autopsy.

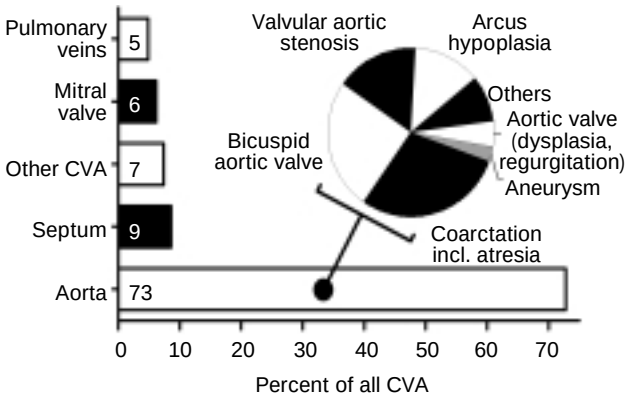

FIG. 1 Synopsis and distribution of cardiovascular anomalies (CVA) in girls with Ullrich-Turner syndrome. The numbers within the columns indicate the exact percentage. The circle diagram illustrates the distribution of aorta-associated malformations.

The distribution within the subgroup with cardiovascular findings revealed a different distribution: 27 of 35 patients (77.1 vs. 54.7%) had monosomy 45 X; only 5 (14.3 vs. 38.5%) had X-mosaic monosomies or X-structural abnormalities (Table III).

Discussion

Congenital cardiovascular diseases and their complications seem to be the most life-threatening in females with Ullrich-Turner syndrome (UTS). Prevalence of CVA varies from 7 to 36% in living patients and 75% in fetuses, respectively. This probably depends on different selection criteria, ascertainment, and small patient numbers.[10] In sonographically evaluated studies, the prevalence ranged from 17 to 26%.[1, 3, 11, 12] In this study we found at least one cardiovascular anomaly (CVA) in 29.9%. Since all patients with cytogenetically diagnosed UTS attended either our endocrinologic or cardiologic outpatient department, there may be a potential bias, inherent in most hospital-based studies. The CVA prevalence in UTS revealed in the Bavarian study, in which data of almost one million children had been analyzed, was 33.3%.[9] Thus, in comparison with this almost unbiased study, our prevalence is within the same dimension, assuming the bias of our study is negligible.

Aortic anomalies were most dominant, representing over two-thirds of all CVA. In 179 Danish females with UTS (mean age 23 years, range 6 months to 46 years), who underwent reevaluation by echocardiography, Gotzsche *et al.* reported bicuspid aortic valves in 14%, aortic coarctation in 10%, and PAPVD in only 0.02%.[1] The Italian study (mean age 11.5 years, range 1 month to 24 years) determined prevalences similar to ours (bicuspid aortic valves in 12.5% vs. 12.8% in our study; PAPVD in 2.9 vs. 3.4%), except for aortic coarctation, which was almost twice as prevalent in our study (6.9 vs. 12.8%).

TABLE III Distribution of karyotypes in all females with Ullrich-Turner syndrome (UTS) compared with those with UTS and cardiovascular anomalies (CVA)

		UTS n = 117		UTS + CVA n = 35	
	Karyotype	N	Prevalence (%)	N	Prevalence (%)
Monosomy	45, X	64	54.7	27	77.1
X-mosaic monosomies	45, X/46, XX, etc.	18	15.4	2	5.7
X-structural abnormalities		27	23.1	3	8.6
Isochromosome	46, X, i(Xp), etc.	8	6.8	1	2.9
Isodicentric chromosome	46, X, idic(Xp), etc.	9	7.7	1	2.9
Ring chromosome	46, X, r(X), etc.	2	1.7	1	2.9
Deletion	46, X, del(Xp), etc.	8	6.8	—	—
Marker chromosome	45, X, +mar	4	3.4	—	—
Exact karyotype unknown		4	3.4	3	8.6

The RR for patients with UTS of having at least one CVA was nearly 50. For determination of RR we compared our prevalence with that in the Bavarian study. As our hospital is also located in Bavaria (the southeast state of Germany, about 12 million inhabitants), we fortunately had an adequate basis for calculating RR in our cohort. In comparison with the CVA prevalence of the general population (0.62%), Bavarian children seem to be at lower risk than the Canadian population (2%).[9, 13] Thus, RR of the Italian study calculated on the basis of the Canadian data may not be comparable with ours. However, the incidence of bicuspid aortic valves was very low among Bavarian children compared with more current studies.[14] Since the data of the Bavarian heart study were ascertained retrospectively in children who had a diagnosed CVA and attended a pediatric cardiologic clinic or department, the real prevalence of a silent CVA such as the isolated bicuspid aortic valve was probably underestimated. Accordingly, the RR of bicuspid aortic valves in UTS might be overrated in this study, even though the evaluation methods were comparable.

Karyotype analysis in all of our subjects revealed a typical distribution, with monosomy 45 X present in 55.7%. In contrast, it was detected in > 77% of the CVA group, showing that its presence indicates a high risk for having CVA; similar results were reported by other groups. Since X-structural anomalies were only observed in two subjects, no conclusions regarding relevant predisposing X-chromosomal regions could be made in this study. However, defining genotype-phenotype correlations is still ongoing and difficult. Genetically informative patients are rare, and even if two patients have the identical partial X-deletion the phenotype can vary.[15] In addition, clinically important CVAs such as coarctation are predominantly found in complete or X-mosaic monosomies. This finding and the usually not excludable presence of mosaicism make planning of phenotype mapping studies difficult.[1, 3, 12, 16, 17] Zinn *et al.* investigated 28 Xp-females (age range 1.3–41.5 years), mapping deletions by fluorescent in situ hybridization (FISH) for several phenotypic features; none of them had CVA.[17]

The short stature homeobox gene (SHOX) is the first and best gene described to be involved in UTS phenotype features. Besides short stature, recent reports indicated SHOX haploinsufficiency may cause most skeletal abnormalities in UTS.[18–20] Associated cardiovascular defects, however, have not as yet been reported.

For development of soft tissue malformations including CVA, several reports indicate that lymphatic hypoplasia and dysplasia may be a possible cause. Following this hypothesis in patients with UTS as well as in those with Noonan syndrome, lymphatic malformations lead to lymphatic stasis and resultant lymphatic distension and lymphedema. This exerts mechanical force on adjacent tissues and organs, which probably causes typical soft tissue anomalies in both syndromes.[21–24] Recently Ogata *et al.* reported a boy with Noonan syndrome and scintigraphically proven, typically located lymphstasis that probably explains most of the adherent soft tissue and cardiovascular anomalies in this patient.[25]

It is inferred that a lymphogenic gene escaping X-inactivation on the sex chromosome is present as a genetic link, and that haploinsufficiency causes lymphatic hypoplasia resulting in soft tissue stigmata. Furthermore, similar anomalies are frequently manifested in patients with Xp and in those with Yp deletions. Thus, it has been suggested that a putative lymphogenic gene is shared by Xp11.4 and Yp11.3.[19, 26, 27]

Even though the same pathophysiologic mechanisms in development of CVA are supposed in patients with Noonan syndrome, no deletions in the Xp or Yp region have been found so far. This may be consistent with the observation of different characteristics of cardiovascular anomalies in both syndromes. In patients with Noonan syndrome CVA occurs predominantly on the right side, with pulmonary valve stenosis being most prevalent; in patients with UTS mainly left-sided defects are found.[28]

Both of our patients (ages 15 and 19) with aortic aneurysm died from dissection.[29] In some but not all patients with UTS with aortic aneurysm, cystic medial necrosis of the aorta similar to Marfan syndrome was found. Generally, multiple risk

factors for development of aortic aneurysm, such as distinct CVA—for example, bicuspid aortic valve or coarctation and systemic hypertension are present in patients with UTS. While in adults hypertension may represent the main risk factor, biochemical defects of the connective tissue have been suggested to be most important in young patients. Corrective surgery of coarctation possibly does not substantially alter the risk of aneurysm. Prophylactic treatment with beta blockers may improve prognosis in these patients.[2, 30–33]

Conclusion

Our data demonstrate that about every third female with UTS is affected with at least one CVA, mainly left-sided and associated with aortic structures. Monosomy 45 X is a harbinger for cardiovascular disease. With respect to the elevated relative risk for CVA in girls and women with UTS, which was calculated on the basis of epidemiologic data in this study, our results underline the necessity of thorough cardiological evaluation. Although no negative effects on the cardiac situation by growth hormone therapy have been reported so far in UTS, we suggest involving a cardiologist in the follow-up of these patients.[34, 35]

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