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Prevalence of cardiovascular malformations in Turner's syndrome

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Report Submitted to fulfill the requirements for Scientific Research Activity

Date of Submission:11/Mar/ 2019

Abstract:

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

Materials and methods:

In March 1988,393 females with Turner's syndrome were registered in the Danish National Cytogenetic Register. They 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 23years (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.

Introduction:

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 chronosome. The syndrome is characterised by shdrt 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, cardio- logy, 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.

Results:

Results from chromosome analysis were available in all. 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 . In 46 (26%) females a total of 69 cardiovascular malformations were found . 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 ($p<0.001$). No cardiovascular malformations were found in the small group with a structural X chromosome abnormality. The association between the cardiovascular malformations and karyotypes . In subjects with 45,X, aortic coarctation was more prevalent than in mosaic monosomy X: 17% v 2% ($p<0.01$). Aortic valve abnormalities were seen in 29 (28%) females with 45, X, but only in four (7%) with mosaic monosomy X ($p<0.001$). Ten (10%) subjects had malformations in more than one cardiovascular site and all had the 45,X karyotype ($p<0.05$). 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. 12 of the 18 with aortic coarctation had previously undergone surgery.

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% .(l-3) This considerable variation probably reflects problems in selection criteria in hospital series and the small sample sizes. 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. 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 l% to 2%. In previous echocardiographic studies the prevalence of bicuspid aortic valve in Turner's syndrome has ranged from 9% to 34%. 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, and indeed 32% of those with bicuspid aortic valve had either stenosis or insufficiency of the valve. The prevalence of aortic coarctation has varied in previous studies from 2% to 19%. We found 10% with aortic coarctation. In the Danish population in general the prevalence is 0.042% . The prevalence of mitral valve prolapse in healthy young women is assumed to be 1% to 2%. An extremely high occurrence of mitral valve prolapse in Turner's syndrome has been found in one study, 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 genotypesl (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. No abnormalities of the aortic valve were found in their study from the pre-echocardiographic era (5). 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 (6).

Conclusion:

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 significant.

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