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Hypertension and ischemic cardiovascular disease in Turner syndrome

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Abstract. Hypertension occurs in many patients with Turner syndrome (TS), probably approaching 50% in aging populations. Hypertension seems to be of the essential type, although the reason for the high frequency is unknown. Hypertension should be looked for, and treated appropriately. Hypertension is probably linked to the frequent occurrence of aortic dissection in TS. Presently, the best drug of choice has not been identified, but usually beta-blockers are recommended. Lipid disorders may be present in some patients and should be treated according to international guidelines. Other risk factors, like an unfavourable body composition should also be looked for and prevented. The presence of ischemic heart disease is increased, and should be monitored during clinical care. © 2006 Published by Elsevier B.V.

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1. Introduction

The presence of congenital malformations such as coarctation of the aorta, horse shoe kidney and pterygium colli in Turner syndrome (TS) is well known, as well as less severe congenital malformations of the heart, especially with the 45,X karyotype. The prevalence and the nature of cardiovascular malformations have been described in several studies [1–3]. The malformations normally involve only the vessels of the left side of the heart, and show a very characteristic pattern when compared with the general population. However, with the possibility of compounding these congenital malformations, it is becoming increasingly clear that hypertension and ischemic heart disease probably also are inherent features of TS.

Here, we review the evidence concerning hypertension and ischemic heart disease.

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2. Hypertension

Thirty percent of girls with Turner syndrome are mildly hypertensive on 24-h ambulatory blood pressure monitoring, and 50% have an abnormal diurnal blood pressure profile [4].

Women with Turner syndrome have significantly elevated blood pressure compared with an age matched control group [5], and as many as 50% have clinical hypertension [6,7]. Treatment with sex hormones caused a significant reduction in the 24-h diastolic and the diastolic day pressure, and a near significant fall in systolic day pressure [5], which we have recently confirmed in a smaller group of patients [8]. The diastolic night/day ratio was elevated compared with controls and increased even further with HRT, as did systolic night/day ratio [5]. The significance of this is difficult to interpret. It is thus evident that women with Turner syndrome are “non-dippers”, i.e., have a diminished reduction of blood pressure during the night [4,5,8]. “Non-dipping” in hypertensive women is a predictor of future cardiovascular events. Twenty-four-hour, day, and night heart rate has been found significantly elevated in Turner syndrome compared to controls [5], which could be suggestive of the presence of parasympathetic neuropathy.

Hypertension in Turner syndrome seems to be essential by nature. At least there is only scant scientific data to suggest that the usual hypertensive female with TS suffers from secondary hypertension. Plasma renin activity has been found to be elevated in approximately 50% of TS girls by some [9,10], whereas others have found normal plasma renin activity and aldosterone levels, as well as normal urinary albumin secretion [8]. In addition, circulating catecholamines are thought to be normal. Renal function is normal in TS in most cases, despite the high frequency of renal malformations [11].

Recently, we found signs of altered autonomic innervation of the heart in TS. Using a battery of conventional bedside tests we found normal cardiovascular responses in comparison with age-matched controls. However, when using short-term spectral analysis of heart rate variability, which is a more sensitive method than bedside tests for detection of early autonomic neuropathy, we found an impaired sympatho-vagal balance or tone in TS [8]. As also found previously, we found an increased heart rate in TS, as well as an impaired response to changing from a supine to a standing position in a combined measure of vagal and sympathetic innervation of the heart. The aetiology behind the defective sympathovagal balance in TS is not clear [8]. In the same study, we also found elevated levels of N-terminal pro-brain natriuretic peptide (BNP), a marker linked to heart failure.

Previous and recent ECG findings show a prolonged QTc segment, suggesting that cardiac conduction and repolarization abnormalities are also intrinsic features of TS [12,13].

Presently there are no longitudinal studies of blood pressure and hypertension in Turner syndrome. There is a definite need for such studies. Furthermore, it is essential to establish the effect of treatment and to determine which drugs to choose as first and second line treatment. The choice of anti-hypertensive drugs is so far based on extrapolations from the experience with Marfan syndrome, and beta-blockers are considered first drug-of-choice, especially given the common tachycardia in TS. In Marfan syndrome, beta-blockers have been shown to be effective in lowering blood pressure and delaying aortic dilatation [14].

However, no prospective studies have documented the efficacy of either beta-blockade or modulation of the ACE/AT-II system in TS.

3. Ischemic cardiovascular disease

3.1. Cholesterol profile

Previously, ischemic heart disease has not been found with increased frequency in Turner syndrome, despite reports of increased levels of cholesterol [15], increased blood pressure, and congenital cardiac malformations.

An epidemiological study found an increased frequency of ischemic heart disease (acute myocardial infarction, and arteriosclerosis) [16]. The relative risk (RR) of disease was increased to 2.1 (95% confidence interval (CI): 1.2–3.4), while hypertension occurred with a RR of 2.9 (95% CI: 1.2–6.0), and cerebrovascular diseases of 2.7 (95% CI: 1.04–5.3). Likewise mortality due to cardiovascular causes is elevated in TS [17].

In a clinical study, we could not detect any difference in measures of lipid status between a group of untreated women with Turner syndrome before treatment and a control group [5,18], also corroborated by others [19], while others, using a different approach in choosing control groups have reached different results. Ostberg et al. used women with premature ovarian failure (POF) as controls, in addition to normal controls, and found an essentially comparable cholesterol profile, including triglycerides, to the cholesterol profile in TS, while normal controls had lower levels of cholesterol [20]. Van et al., using the same approach with a POF control group, found an elevated cholesterol profile in TS [21], with a reduced LDL size, suggesting a more atherogenic lipid profile. Suffice to say, additional research is necessary to conclude whether the lipid profile in TS is normal or elevated.

Compensated hypothyreosis is, however, often a problem in TS, and is associated with coronary artery disease, and elevated fractions of cholesterol [22]. This may help explain part of the increased risk of cardiovascular disease in Turner syndrome [16], since hypothyreosis and thyroid antibody formation is common in Turner syndrome.

3.2. Left ventricular function

Since women with TS are at risk of not only congenital cardiovascular malformations but also hypertension and ischemic heart disease, left ventricular (LV) performance may also be perturbed. Conventional echocardiography, however, has not been able to identify LV dysfunction in TS [1,23] but the techniques used may well have been insufficient to detect subtle alterations in cardiac function.

We have recently introduced tissue Doppler echocardiography in the study of LV function in TS, which is more sensitive in detection of the early phases of systolic dysfunction, particularly in the assessment of longitudinal myocardial dysfunction. [24,25]. We examined 33 young, normotensive, healthy TS, only using HRT, and 33 age-matched controls, and found LV diastolic dysfunction in more than a quarter of the women with TS [38]. It is quite remarkable to find diastolic dysfunction in such a young group of women, normally only present in patients with considerable LV hypertrophy [26], myocardial infarction or reduced LV ejection fraction [27]. The presence of diastolic dysfunction was

closely related to the increased heart rate seen in TS, possibly related to some degree of autonomic cardiac neuropathy (see above). Systolic LV function was also impaired in the TS group, and closely related to the impaired diastolic function. The coexistence of impaired relaxation and decreased systolic performance has previously been seen in hypertensive patients and in patients with diabetes mellitus, irrespective of blood pressure levels [28]. In such cases, the presence of increased LV mass concomitant with poorer metabolic control seems explanatory [29]. However, in this population of normotensive women with TS, only a vague relation between the metabolic control and markers of left atrial (LA) pressure (LA index and the A-wave velocity) was seen. Similarly, no relations between LV systolic performance and metabolic control or LV geometry were found. This may relate to the narrow range of normal insulin sensitivity in this group. In contrast, LV global stiffening was reflected in both diastolic and systolic performance, determined by two different modalities (Fig. 1). Myocardial stiffening in women with TS may be due to an intrinsic myocardial component, which could be a primary defect in TS leading to left ventricular inadequacy over time [30].

3.3. Other cardiovascular risk factors

C-reactive peptide (CRP) is a marker of a chronic inflammatory state, as often found in ischemic heart disease, and has been found to be elevated in TS [20,31]. Likewise, Ostberg et al. found elevated levels of interleukin-6 (IL-6), a marker linked to both visceral fat and ischemic heart disease. We have recently corroborated these findings, and in addition, we found elevated levels of other adipokines like IL-8 and TNF- α , but paradoxically normal levels of adiponectin (unpublished observations, CH Gravholt et al.).

In addition, body composition in TS is profoundly changed. Fat mass and body mass index have been found to be higher in adult Turner patients compared with age matched controls, and lean body mass (LBM) is inappropriately low [32,33]. In addition, distinct

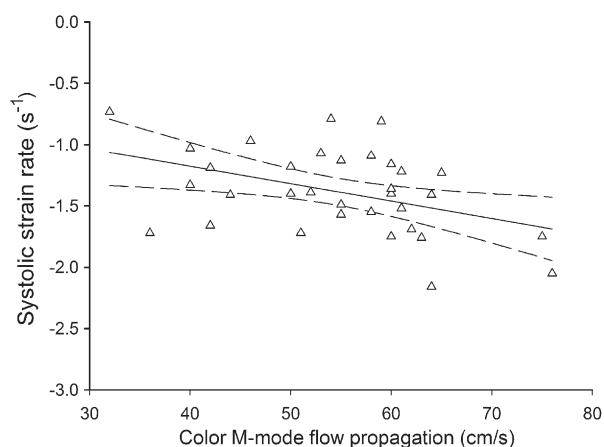


Fig. 1. Correlation between systolic strain rate and velocity flow propagation (a measure of diastolic function) in women with Turner syndrome.

differences in regional body composition is present in young TS girls (9–15 years) in comparison with age- and BMI-matched controls in two different study groups [34,35], and in adults excess visceral fat and hepatic adipose tissue has been documented [36], and imprinting of the one X chromosome, with inheritance of the maternal X chromosome being more deleterious, has also been suggested [37]. TS has therefore been characterized as a syndrome of disproportionate anthropometry and body composition [35].

4. Conclusion

Hypertension occurs in many patients with TS, probably approaching 50% in aging populations. Hypertension should be looked for, and treated appropriately. Lipid disorders may be present in some patients and should be treated according to international guidelines. Other risk factors, like an unfavourable body composition should also be looked for and prevented. The presence of ischemic heart disease is increased, and should be monitored during clinical care.

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