Systemic hypertension, ischemic heart disease, and stroke are major factors that reduce lifespan in Turner syndrome. Importantly, high blood pressure (BP) is the most readily treatable risk factor for aortic dissection and rupture that occurs in young women with Turner syndrome. A review of 65 cases of aortic dissection in girls and women with Turner syndrome identified concomitant congenital heart disease and hypertension in 89%, with half of cases occurring before age 30. Unfortunately, systemic hypertension occurs frequently in Turner syndrome with prevalence estimates of 25% to 40% in girls and an even larger percentage in affected women. Having few overt symptoms, high BP can easily go unrecognized. Elevated BP by casual BP measurement is common in the general child and adolescent population, with estimates of 10% to 17%; however, the overall burden of true hypertension, further study may provide clues to genetic factors leading to a better understanding of essential hypertension in the general population.

Key Words: aortic coarctation ■ high blood pressure ■ hypertension ■ obesity ■ Turner syndrome

Subjects and Methods

The protocol was approved by the Institutional Review Board at Oregon Health & Science University. As part of the ongoing Turner Syndrome Healthy Heart Project at the annual meeting of the Turner Syndrome Society of the United States from 2003 to 2011, 168 volunteer subjects aged 2 to 17 years with Turner syndrome participated in cardiovascular health screening. Written consent was obtained from all subjects or their legal guardians, and a written assent obtained from children capable of reading the form.

Subjects completed a standardized questionnaire documenting karyotype (45,X versus non-45,X), history of growth hormone use, thyroid disease, renal/urologic disease, surgical repair of aortic coarctation, and self-reported history of a diagnosis of hypertension. Height and weight were measured. A single screening BP was measured after a short period of rest (3–5 minutes) in seated position on the right upper arm by automatic oscillometry (Dynamap, GE Healthcare) using methods consistent with American Heart Association recommendations. Taking the BP on the right arm minimized the possibility of or erroneous measurement in subjects who had previous aortic coarctation operations. Focused 2-dimensional echocardiography was performed with a Philips Sonos 5500 or IE 33 (Philips Medical Systems, Bothell, WA) ultrasound system. Age and height-adjusted systolic BP percentiles (n=168) and age-adjusted body mass index percentiles (n=166; 2 subjects not weighed) were calculated. BP ≥95th% was considered evidence of potential hypertension (consistent with definition of stage 1 hypertension or greater). Body mass index ≥95th% was considered to be obesity.

Statistical analysis was conducted using SAS software. Univariate comparisons were made by χ² and Fisher exact test to identify factors associated with hypertension. P<0.05 was chosen as the level of statistical significance.
Results

One hundred sixty-eight individuals aged 2 to 17 years were studied. Prevalence of reported clinical features is shown in Table.

45,X occurred in 44% of (74/168) subjects. The remaining 56% (94/168) were classified as non-45,X karyotype. These subjects represent a heterogeneous group that potentially includes deletions, translocations, mosaics, rings, duplications, or other configurations that were not specifically reported in the questionnaire. Surgical repair of aortic coarctation occurred exclusively in the newborn period. No subject had residual coarctation by Doppler echocardiography.

The prevalence of elevated screening BP (systolic and diastolic) was 42.3% (71/168), while only 7.7% (13/168) reported a history of hypertension. Prevalence of elevated screening systolic BP was 35.7% (60/168). Of those who self-identified a history of hypertension, 46% (6/13) had measured BP <95th%.

Prevalence of systolic BP ≥95th% was greater in those with history of repaired aortic coarctation (51.7% versus 32.4%; P=0.0479) and odds ratio of 2.24 (95% confidence interval 1.00–5.03). As expected, significant hypertension was more common in obese compared with nonobese subjects (58.1% versus 31.1%; P=0.0048) and odds ratio of 3.07 (95% confidence interval 1.38–6.83; Figure). Prevalence of obesity, growth hormone use, renal/urologic disease, and thyroid disease were equivalent between those with and without history of aortic coarctation. Systolic BP ≥95th% was not significantly associated with aortic size dimensions. 45,X karyotype was associated with history of aortic coarctation (data not shown). Prevalence of obesity in the sample population was 18.7%.

Discussion

The principal finding of this study is that elevated screening BP occurs in 42% of girls with Turner syndrome, far greater than the prevalence of hypertension in the general pediatric population or in studies screening for elevated BP.10,12,15–17 We have included more subjects than most other Turner syndrome-specific studies, and the high prevalence we observed is consistent with these studies.1,3–7 Furthermore, our results strongly suggest that there is a BP awareness gap in Turner syndrome. This is likely because of a combination of factors, including inadequate screening, lack of appreciation for the significant health risks posed by hypertension once it is diagnosed, and inadequate treatment or follow-up. In our study, a minority (<1 in 5) with elevated screening BP had previously been diagnosed with hypertension, and of those actually diagnosed with hypertension, the majority still had elevated BP, suggesting inadequate treatment. Addressing each of these barriers to effective screening, diagnosis and treatment will be required to reduce the burden of hypertension in Turner syndrome.

As in the general population, repaired aortic coarctation, even without residual obstruction, is a significant risk factor for high BP in Turner syndrome.18 Even a brief period of systemic hypertension may induce chronic vascular changes that manifest later in childhood as hypertension. Coarctation of the aorta is usually repaired in the neonatal period, suggesting that pre- or early postnatal hypoperfusion of the kidneys may play a pathogenic role. This may involve maturation of nephrons, regulation of neuroendocrine hormones, or other factors that impact long-term BP regulation.19 A vasculopathy intrinsic to Turner syndrome has been hypothesized; coarctation may amplify these risks. Women with Turner syndrome have greater intima–media thickness and artery diameters. Because estrogen deficiency contributes to intimal thickening, estrogen replacement may be a modulator of cardiovascular risk in this population.20

Obesity is well-recognized to be associated with hypertension in the general pediatric population. It is noteworthy that the prevalence of obesity in our sample population is similar to national estimates for all girls (18.7% versus 17.2%).21 Classification of obesity in our study was associated with elevated BP with OR 3.07, which is within the range previously reported for obese versus nonobese girls in the general population, 1.96 to 4.20.8,15–17,22 The high prevalence of elevated BP in our subjects, despite a comparable degree of obesity, suggests that the Turner syndrome population is sensitized for hypertension. Indeed, even in those without a history of coarctation or obesity, nearly one third had elevated screening BP. Taken together, these data invite the hypothesis that Turner-specific pathways for essential hypertension are discoverable. In this regard, it is interesting that in the general population, female sex seems to protect against high BP,23 an effect that may not be solely attributable to gonadal sex.24 Importantly, there may be protective genes unrelated to sexual differentiation present on the second sex chromosome that are deficient in those living with Turner syndrome.25 An additional hypothesis is that haplinsufficiency of critical genes on the X chromosome (gene dosage effect) may interact with autosomal variants that will be identifiable through genotype–phenotype correlation studies.26 Candidates for these genes may relate to the established Turner syndrome vasculopathy,20,27,28 dysregulation of the sympathetic nervous system, or abnormalities of diurnal BP variation.5,6,29

Although it is established that estrogen plays a significant protective role in the control of BP in the premenopausal years, the opposite may be true post menopause.24 Importantly, in our study, there were no differences in estrogen replacement therapy when those with increased BP were compared with those with normal BP. It is of interest that there are sex chromosomal effects that occur independently of the gonadal

<table>
<thead>
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<th>Feature</th>
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<tr>
<td>45,X karyotype</td>
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<tr>
<td>Obesity*</td>
<td>31</td>
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<tr>
<td>History of renal or urologic disorder</td>
<td>21</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*Weight/BMI not recorded for two subjects. Data reported include 166 subjects. BMI indicates body mass index.
hormones. Studies that use the four core mouse model where gonadal sex is genetically segregated from chromosomal sex suggest that the 46,XX karyotype may harbor an adverse effect on BP that may be unmasked in the setting of 45,X.32

Growth hormone treatment increases growth velocity as well as final adult height in Turner syndrome.30–32 The definition of elevated BP in children depends on height, and therefore, the effect of growth hormone treatment on prevalence of elevated BP may be modulated in part by a gain in linear growth. However, this effect is likely small because the difference in threshold of elevated BP in a child at the 5th versus 25th height percentile (equivalent to average gain in final adult from growth hormone treatment) is 0 to 2 mm Hg depending on age.33 Long-term follow-up studies of the effect of growth hormone on BP in Turner syndrome show slight decrease in diastolic BP,32,33 a finding reflected in a large meta-analysis of trials studying adults treated with growth hormone for growth hormone deficiency.34

The design of our study is limited by the inclusion of subjects who chose to attend a national conference which may suggest increased health literacy, advocacy, and financial means and, therefore, may not be entirely representative of the general Turner syndrome population. The self-reported medical history is subject to recall bias. We recognize that a single ambulatory BP screening is not diagnostic of hypertension, though it may most closely represent the real-life clinical environment in identifying the population at risk. In this study, we identified a large cohort that have a high pretest probability of true hypertension that should be validated through 24 hour ambulatory BP monitoring. Ongoing observation of this large cohort will permit longitudinal analyses of incidence and may potentially lead to an understanding of fundamental mechanisms of essential hypertension in the general population.

Perspectives

Our study suggests that Turner syndrome alone carries with it an increased intrinsic risk for hypertension, which may play a substantial role in the previously reported excess risk for cardiovascular morbidity and mortality. Aortic coarctation repair (even in those without residual obstruction) and obesity increase the risk for hypertension further. Targeting modifiable risk factors (obesity), intensive surveillance of high-risk subgroups (history of aortic coarctation), and early and intensive treatment of hypertension has the potential to reduce the burden of cardiovascular disease in Turner syndrome. Although obesity plays a significant role in hypertension risk, our data suggests the prevalence of obesity is not different in the Turner syndrome population than the general population. This observation invites the hypothesis that genes on the second sex chromosome may interact with gene variants on autosomal genes to cause essential hypertension. An understanding of the biological pathways controlled by these genes could lead to important clues regarding mechanisms of essential hypertension in the general population.

Acknowledgments

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Divisions of Pediatric Endocrinology and Cardiology research accounts.

Disclosures

None.

References

What Is New?

- The prevalence of obesity in Turner syndrome is no different than the general population, yet there is a significantly higher rate of hypertension. This observation suggests the novel hypothesis that Turner-specific pathways for essential hypertension are discoverable and could serve as treatment targets in the general population.

- In girls with Turner syndrome, high blood pressure is prevalent and associated with obesity and history of corrected aortic coarctation. Most with high blood pressure are unaware.

What Is Relevant?

- The high prevalence of hypertension in those who live with Turner syndrome significantly contributes to their excessive risk for death, aortic dissection, myocardial infarction, and stroke. Targeting modifiable risk factors (obesity), intensive surveillance of high-risk subgroups (history of aortic coarctation), and early and intensive treatment of hypertension has the potential to reduce the burden of cardiovascular disease in Turner syndrome.

Summary

Identification of risk factors associated with hypertension is critical to reduce cardiovascular morbidity and mortality in Turner syndrome. Because those with Turner syndrome are sensitized for hypertension, it may be easier to discover disease-causing genes that play a role in the pathophysiology of essential hypertension in the general population.
Pilot Study of Blood Pressure in Girls With Turner Syndrome: An Awareness Gap, Clinical Associations, and New Hypotheses
Evan Los, Emilio Quezada, Zunqiu Chen, Jodi Lapidus and Michael Silberbach

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