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Growth hormone treatment and left ventricular dimensions in Turner syndrome

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Abstract

Objective—To determine if cardiac dimensions were different in girls with Turner syndrome (TS) that did receive growth hormone (GH) vs. those who did not receive GH.

Study design—This was a retrospective, cross sectional study analyzing echocardiograms in 86 females with TS divided into GH-treated (n=67) vs. untreated (n=19) groups. These were subjects with TS participating in the National Institutes of Health protocol between 2001 and 2006.

Results—The average age was 16.2 years (range 10-25 yrs) and duration of GH treatment was 4.4 (range 1-14 yrs). The GH-treated group was taller by ~6 cm ($P=0.004$) but, cardiac dimensions normalized to body surface area (BSA), including septal and posterior wall thicknesses, left ventricular (LV) mass and LV internal diameters, were not significantly different in the two groups. The fractional shortening index was similar in the two groups. Multiple regression analyses indicated that BSA, but not duration of GH treatment predicted LV dimensions in girls with TS.

Conclusions—GH treatment of girls with TS increases stature but does not disproportionately affect cardiac dimensions.

Keywords

echocardiography; growth hormone; cardiac dimensions; Turner Syndrome

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Turner syndrome (45,X, TS) is the most common chromosomal disorder in females, occurring in ~1/2500 live female births (1). Short stature and ovarian failure are the most prevalent findings, but the most medically significant feature is congenital heart disease with a high risk for aortic dilatation and dissection(2-4). In addition to anatomical defects, recent studies have demonstrated electrocardiographic abnormalities and evidence of autonomic and diastolic dysfunction in individuals with TS suggesting a more extensive involvement of the cardiovascular system than previously appreciated (5-8). Although girls with short stature in the context of TS are not usually growth hormone (GH) deficient, the FDA has approved treatment of these girls with recombinant human GH to augment adult height (9-12). Girls with TS are typically treated with GH for ~5 years using pharmacological doses higher than those normally used in GH-deficient states.

GH actually promotes generalized somatic growth and has significant direct and indirect effects upon the cardiovascular system (13). GH excess resulting from tumors produces an increased heart rate and cardiac output in early stages, followed by cardiac hypertrophy and eventually cardiomyopathy (13). Aortic and mitral regurgitation and arrhythmias are also more prevalent in individuals with acromegaly. GH treatment of GH-deficient individuals increases cardiac mass and output (14,15). Treatment of normal volunteers with GH doses similar to those used in TS (0.06 mg/kg/d) increased cardiac output and left ventricular mass in just 4 weeks (16). Finally, treatment of GH-deficient children with exogenous GH has been associated with disproportionate left ventricular growth (17,18). Given the cardiac involvement in TS there has been concern over potential adverse cardiovascular effects of GH treatment. Two echocardiography studies reported “normal” left ventricular morphology and function in GH-treated girls with TS (19,20); however, these studies had no untreated girls with TS for comparison. In the present retrospective study, we examined cardiac variables using echocardiography in girls with TS that received GH treatment and compared them with a group that were not treated.

Methods

Study subjects

Study participants were part of the Turner Syndrome natural history protocol which was approved by the National Institute of Child Health Institutional Review Board. All adult participants and parents of minor children gave written informed consent and minors informed assent. The protocol includes studies of bone mineral density, metabolic function and cardiovascular imaging. Study subjects were mainly recruited through notices on the NIH website <http://turners.nichd.nih.gov/>. Inclusion criteria were phenotypic females older than 6 years who had a 50 cell peripheral karyotype in more than 70% of cells that demonstrate loss or partial loss of the second sex chromosome.

Consecutive participants between the ages of 10 to 25 and parents of minors were queried on their use of GH. Twenty-one subjects had not received GH treatment compared to 67 who did receive GH treatment. The usual daily dose for our patients was 0.05 mg/kg/d. Height and weight for each subject were measured by NIH Clinical Research Center (CRC) nurses using a SRSscale®, model SR555, with a height rod. Body mass index (BMI) and BSA were calculated using the DuBois and DuBois formulae.

Echocardiography

Transthoracic 2D and Doppler echocardiography was obtained on all subjects using commercially available echocardiography machines. The standard parasternal, apical, and subcostal views were obtained with the participants in the left lateral recumbent position. The images were stored digitally and on VHS videotape for analysis. Cardiac measurements were

performed according to the American Society of Echocardiography guidelines(21). The left ventricular mass (LVM) was calculated using the following anatomically, validated formula, where IVS is interventricular septal thickness, PW is posterior wall thickness, and LVIDD is left ventricular internal diastolic dimension (22): $LVM (g) = 0.8 (1.04 [IVS + PW + LVIDD]^3 - [LVIDD]^3) + 0.6$. LVM was divided by BSA (m^2) to adjust for the effect of body size (23).

Statistics

Data are presented as means with standard deviations. Group means were compared by ANOVA, with age and body size variables as covariates as indicated followed by the Fisher's PLSD test. Multiple linear regression was used to analyze the effects of GH on cardiac dimensions. Analyses were performed using Stat View for Windows, version 5.0.1 (SAS Institute Inc., Cary, NC).

Results

Study subjects

There were 86 study subjects aged 10-25 years with reliable information on GH use. Of these, 19 had never used GH and 67 (78%) had used GH for one year or more. The most common reason for not using GH was late diagnosis, followed by satisfaction with the patient's height. The average duration of GH use was 4.4 yrs (range 1 – 14 yrs). Twenty-three subjects were still taking GH at the time of their echocardiograms. Of the 67 subjects who received GH-treatment, one had hypertension, 16 (24%) had a bicuspid aortic valve and 2 had a history of coarctation of the aorta. Of the 19 subjects not treated with GH, one had hypertension, 3 (16%) had a bicuspid aortic valve and none had coarctation. None of the subjects had significant aortic or mitral regurgitation. The two groups were similar in age and body mass, but the GH-treated group was significantly taller (Table I).

Effect of GH on cardiac dimensions

The effect of GH status on cardiac dimensions is also reported in Table I. All the measures were within the normal age group range. To adjust for body size differences, cardiac dimensions were normalized to BSA. There were no significant differences in any cardiac measures in the GH-treated vs. untreated groups (Table I). Fractional shortening, a measure of LV function, was also similar in the two groups. In addition, measures of diastolic function, E/A ratio (peak flow velocity in early diastole (E wave) and peak velocity at atrial contraction (A wave) and mitral deceleration time (DT), were normal and not significantly different between the groups. We further investigated if the *duration* of GH treatment affected cardiac dimensions. Thus, we used multiple regression analyses to evaluate the duration of GH treatment along with age and BSA as covariates (Table II). These analyses indicated that the number of years on GH did not independently influence cardiac growth. We also performed this analysis on the group currently on GH (n=23) and obtained similar results (not shown).

Discussion

This study investigated the effects of GH treatment lasting an average of 4-5 years on cardiac dimensions in girls and young women with TS, using echocardiography to compare LV wall thickness and diameters in the 2 groups. As expected, the GH-treated group was significantly taller and cardiac dimensions were correspondingly increased compared to age-matched untreated subjects. Adjusting for their larger body size, there were no significant differences in cardiac dimensions in the two groups. The fractional shortening, an index of LV function, was also similar in the two groups. These findings show that cardiac size in GH-treated girls with TS is proportionate to their increase in body size, suggesting that GH treatment, even in

pharmacological doses, does not produce abnormal cardiac growth or hypertrophy in girls with TS.

An earlier study investigated the effects of 3 dosages of GH over 7 years in Dutch girls with TS, also by echocardiography (20). There was no untreated control group in this study, but cardiac dimensions were within the normal range for these girls and there was no apparent GH dose effect seen in the three different dosage groups. Another study compared cardiac measures in GH-treated girls with TS vs. age and size matched eukaryotic girls (24). They found no difference in LV mass or volume, but did report mild diastolic dysfunction among subjects with TS. However, these differences were likely attributable to significant differences in heart rate and blood pressure between the two groups. It is well established that the heart rate and blood pressure are on average higher in girls with TS compared to age-matched controls (25).

Although it is advantageous to have an untreated group with TS for comparison, a major drawback of our study is that groups were not randomly assigned. Thus there could be selection bias contributing to the findings. For example, if girls with cardiac involvement were selectively excluded from GH treatment by their caregivers, then the comparison might not be valid. However, the frequency of cardiovascular defects was similar in the two groups, e.g., about 20% of each group had a bicuspid aortic valve. Also, it was abundantly clear that the major reason for non-treatment was late diagnosis because of suboptimal medical care, since the untreated girls were very short and generally as severely affected as the treated group. Finally, it is possible that adverse cardiovascular effects may not be apparent until more time has passed, and hence more long term follow-up is necessary to confirm the finding of no harmful effects of GH treatment on the cardiovascular system of patients with TS.

Our study establishes that pharmacological GH treatment has little effect upon LV size in patients with TS, at least over an intermediate (4-5 yr) period of observation. Thus we confirm the earlier studies that lacked control groups with TS, and extended our own previous study showing no apparent effect of GH on aortic diameter in TS (26). It is curious that there seems to be no cardio-selective effect by GH in girls with TS, although GH treatment of GH-deficient children has been associated with disproportionate left ventricular growth (17,18). Perhaps this is because in GH deficiency there is a relative cardiac hypoplasia and associated catch-up growth with GH treatment. In any case, the present findings are reassuring that girls with TS are not especially vulnerable to GH-induced cardiac hypertrophy.

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Table 1

Somatic and Cardiac Dimensions in GH-treated vs. untreated patients with TS

	No GH (n=19)		Treated with GH (n=67)		P value
	Mean/SD	Range	Mean/SD	Range	
Age (years)	16.5/4.8	10-25	16.1/4.3	10-25	0.727
Height (cm)	138.6/11.2	115.0-157.1	145.7/9.4	122.0-162.7	0.004
Weight (kg)	47.4/16.4	25.8-96.4	50.1/13.8	24.2-84.9	0.309
BMI (kg/m ²)	24.2/5.7	15.6-39.1	23.3/4.9	15.4-39.4	0.855
BSA (m ²)	1.3/0.2	1.0-2.0	1.4/0.2	0.9-1.9	0.070
Septum/BSA (mm/M ²)	5.4/0.9	4.1-6.3	5.2/0.8	3.7-7.4	0.367
Posterior Wall/BSA (mm/M ²)	5.4/0.9	4.1-6.3	5.1/0.7	3.5-6.6	0.057
LVID diastole/BSA (mm/M ²)	30.5/4.4	22.0-39.8	30.5/4.4	22.4-41.3	0.970
LVID systole/BSA (mm/M ²)	19.2/2.2	15.4-22.5	19.1/3.4	12.0-27.9	0.948
LV mass/BSA (g/M ²)	59.1/16.2	39.3-108.8	63.4/12.5	40.6-90.7	0.224
Fractional Shortening (%)	36.1/8.1	27.0-50.0	37.6/6.1	25.0-53.7	0.422
E/A ratio	1.8/0.6	1.0-3.2	1.7/0.5	1.1-3.4	0.319
DT	125.1/36.3	80.7-208.0	140.8/68.0	63.6-451.0	0.409

Mean values compared by ANOVA, with age as covariate followed by Fisher's PLSD test. Cardiac measurements are normalized to BSA. Fractional shortening = (LVID-LVIS)/LVID.

Table II

Effect of GH Treatment on Septum, PW, LVID diastole, LVID systole, and LV mass Controlling for Age, Years on GH, and BSA

Cardiac Dimension	Estimate	SE	t ratio	p value
Septum $R^2 = 0.246$, $p = 0.0004$				
n=67				
Intercept	3.604	0.814	4.430	<0.0001
Age	0.013	0.039	0.335	0.739
Years on GH	0.002	0.043	0.042	0.966
BSA	2.363	0.800	2.952	0.004
PW $R^2 = 0.409$, $p < 0.0001$				
n=67				
Intercept	2.643	0.679	3.892	0.0002
Age	-0.003	0.033	-0.092	0.927
Years on GH	-0.005	0.036	-0.138	0.891
BSA	3.172	0.668	4.748	<0.0001
LVID diastole $R^2 = 0.222$, $p = 0.001$				
n=67				
Intercept	29.230	3.147	9.288	<0.0001
Age	0.045	0.151	0.300	0.765
Years on GH	0.032	0.166	0.193	0.848
BSA	8.422	3.096	2.720	0.008
LVID systole $R^2 = 0.116$, $p = 0.050$				
n=67				
Intercept	20.344	2.817	7.223	<0.0001
Age	0.022	0.135	0.162	0.872
Years on GH	0.232	0.149	1.559	0.124
BSA	3.140	2.771	1.133	0.261
LV mass $R^2 = 0.017$, $p = 0.778$				
n=67				
Intercept	80.418	20.737	3.878	0.0003
Age	-0.954	0.996	-0.958	0.342
Years on GH	-0.401	1.094	-0.367	0.715
BSA	14.317	20.399	0.702	0.485