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Prolongation of the Cardiac QTc Interval in Turner Syndrome

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Abstract: Anatomic anomalies of the cardiovascular system occur in ~50% of individuals with Turner syndrome (TS), with the specific genetic cause(s) for the heart defects still unknown. Because congenital heart disease may be associated with conduction system abnormalities, we compared electrocardiograms (ECGs) in 100 women with TS and 100 age-matched female controls. Women with TS were significantly more likely to demonstrate left posterior fascicular block ($p < 0.005$), accelerated AV conduction ($p < 0.006$), and T wave abnormalities ($p < 0.006$). The PR interval was significantly shorter (137 ± 17 vs. 158 ± 18 ms, $p < 0.0001$) and the rate-corrected QT interval (QTc) significantly longer in women with TS than in controls (423 ± 19 ms vs. 397 ± 18 ms; $p < 0.0001$). Twenty-one women with TS but no controls had a QTc greater than 440 ms. We found no statistically significant relation between body habitus, cardiac dimensions, evidence of congenital heart disease, or metabolic parameters and the incidence of ECG abnormalities or QTc duration in TS.

Cardiac conduction and repolarization abnormalities appear to be intrinsic features of TS, suggesting that deletion of the second sex chromosome has more profound effects on the cardiovascular system than previously recognized, and that ECG analysis should be included in evaluating and monitoring patients with Turner syndrome.

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Abbreviations: ECG = electrocardiogram, LVH = left ventricular hypertrophy, LVM = left ventricular mass, MR = magnetic resonance, MRA = magnetic resonance angiography, NICHD = National Institute of Child Health & Human Development, QTc = QT interval corrected for heart rate, TS = Turner syndrome.

INTRODUCTION

Turner syndrome (TS) is caused by partial or complete absence of a second sex chromosome and affects ~1/2000 live female births[24]. Characteristic features include short stature, premature ovarian failure, webbing of the neck, and congenital cardiovascular defects[18]. Congenital heart defects most commonly include bicuspid aortic valve and coarctation of the aorta, which affect approximately 15%–20% of patients[11,13,20,29]. Less common defects include persistent left superior vena cava and partial anomalous venous return (~13% each)[2,13], with septal defects or other anomalies much less common. There is little knowledge about the specific genetic basis for heart defects in TS. One school of thought suggests that they are secondary to fetal lymphedema causing impaired filling or compression of nascent outflow structures[5].

Recent research has revealed that genetic defects leading to congenital abnormalities of cardiovascular development may also be associated with diffuse myopathic changes accompanied by conduction defects in adults—apart from the presence or repair of congenital heart defects[26]. Previous cardiovascular investigations in TS have focused on the detection of congenital heart defects, but electrocardiogram (ECG) findings are not usually reported. To the best of our knowledge, there have been no systematic studies on electrocardiographic patterns in TS. We were impressed with a seemingly very high prevalence of abnormal ECG tracings in girls and women with TS participating in our ongoing study of genotype-phenotype relations in this disorder. In most cases, we could find no conventional explanation for the abnormal ECG. Therefore, in the present study, we compared ECG findings in 100 women with TS and 100 age-matched women volunteers without TS.

METHODS

Study Subjects

Women with TS were participating in an ongoing intramural National Institute of Child Health & Human Development (NICHD) protocol at the National Institutes of Health (NIH) Clinical Research Center. All study subjects signed informed consents approved by the NICHD Institutional Review Board. Criteria for entry into the TS study include a 50-cell karyotype by G-banding, with >70% of cells showing absence or abnormality of the second sex chromosome in girls and women aged 7–70 years. The karyotype distribution for the subjects with TS was approximately 62% 45,X; 15% mosaic 45,X/46,XX; 12% 46,X,i(Xq) or mosaic 45,X/46,Xi(Xq); 4% 46,X,del(Xp) with the remainder 45,X with mosaicisms for ring X, or a Y chromosome. All study subjects were off estrogen/progestin treatment for 2 weeks before admission and were euthyroid

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during the evaluation. The first 100 adult women with TS (average age, 35 ± 11 yr) enrolling in the NICHD protocol were included in this analysis. Study subjects were recruited through NICHD (http://turners.nichd.nih.gov/ProtFrNewProtocols.html) and Turner Syndrome Society USA website announcements. These announcements do not specifically feature cardiovascular evaluation as part of the study.

Women who volunteered as controls were participants in clinical studies through the NIH normal volunteer enrollment program, with normal physical exams and normal results on routine laboratory evaluations, and 100 were selected based on age-matching to the TS population.

Electrocardiograms

Standard 12 lead ECGs were obtained using the Hewlett Packard Pagewriter XLI 1700A machine. All ECGs were recorded at 25 mm/s with an amplitude of 1 mV/10 mm and with 60 Hz filtering. They were analyzed using Pagewriter A.04.01 ECG analysis software (Philips Medical Systems, Andover, MA). The QT interval measurement in this program is made by averaging the 5 longest QT intervals with a T or T′ wave amplitude greater than 0.15 mV. All ECGs were over read by a single cardiologist (DRR) in a blinded fashion in the analyses performed in this study.

The following definitions were employed in this study:

Normal PR interval: 120–200 ms

Normal QRS duration: $\leq$100 ms

Normal QT interval corrected for heart rate (QTc): $\leq$440 ms[1,3]

Abnormal ST segment: $\geq$1 mm ST depression 80 ms after the J point

Abnormal T waves: limb leads - QRS-T angle >60°, precordium - T <10% of the height of the QRS or negative in configuration (except in V1)

Left anterior fascicular block (left axis deviation): QRS axis in the limb leads < −30°

Left posterior fascicular block (right axis deviation): QRS axis in the limb leads >90°

Poor R wave progression: Failure of R waves to increase in amplitude in any 2 consecutive leads V1-V3

Early transition: R/S ratio >1 in lead V2

Late transition: R/S ratio <1 in lead V5

Left ventricular hypertrophy (LVH): Sokolow-Lyon[34], Cornell[4], or Romhilt-Estes[32] criteria

Right ventricular hypertrophy: R/S ratio in V1 >1, RV1 >7 mm, R′V1 >10 mm, or in RBBB R′V1 >15 mm

Left atrial abnormality: terminal negativity of P wave in V1 at least 0.1 mV in depth and 40 ms in width

Right atrial abnormality: P wave in lead II $\geq$0.25 mV

Low voltage: all limb leads <0.5 mV or all precordial leads <1.0 mV

Magnetic Resonance Characterization of Congenital Cardiovascular Anomalies and Chest Dimensions

Magnetic resonance (MR) exams were performed on a 1.5 Tesla MR Scanner (Signa, General Electric Medical Systems, Waukesha, WI) equipped with high-performance gradients and using a phased array coil. Imaging included axial and coronal T1-weighted fast spin echo and oblique sagittal fast gradient echo pulse sequences. Gadolinium (Gd)-enhanced 3-dimensional MR angiography (3D MRA) was performed using a fast 3D spoiled gradient echo pulse sequence and 0.2 mmol/kg dose of Gd-chelate contrast media. Following the Gd-enhanced 3D MRA, axial fat suppressed spoiled gradient echo images were also obtained. The MR and MRA images were evaluated by a single cardiovascular radiologist (VBH) and have been previously described[13]. Thoracic dimensions were measured in each subject using T1-weighted fast spin echo images and included the maximum superior-to-inferior dimension (SI), maximum anterior-to-posterior dimension (AP), and maximum right-to-left dimension (RL). Thoracic volume was calculated from MR measurements of internal thoracic dimensions using the equation of a half ellipsoid: thoracic volume (m^3) = $1/2 \times 4/3 \times \pi \times SI \times AP \times RL$.

Echocardiogram for Left Ventricular Mass Assessment

All subjects underwent transthoracic 2D and Doppler echocardiography using commercially available echocardiography machines. Standard parasternal, apical, and subcostal views were acquired with the patients in the left lateral recumbent position and were stored digitally and on VHS videotape for analysis. Evaluation of the echo images was performed blinded to each subject's clinical presentation and past cardiovascular history. Cardiac measurements were performed according to the American Society of Echocardiography guidelines[33]. 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[9]: LVM (g) = 0.8 (1.04 [IVS + PW + LVIDD]^3 − [LVIDD]^3) + 0.6. LVM was divided by height to the power 2.7 (g/m$^{2.7}$) or by BSA (m^2) to adjust for the effect of body size[7].

Laboratory Tests

Routine fasting blood chemistries including electrolytes, minerals, lipids, and thyroid tests were obtained for each subject with TS. These assays are described on the NIH Clinical Center Lab Directory website (http://cclnprod.cc.nih.gov/dlm/testguide).

Blood Pressure

During their inpatient evaluation, women with TS had 24-hour ambulatory blood pressure monitoring using Welch-Allyn QuietTrak[37] monitors (Model 6783–6100; Tycos-Welch-Allyn, Arden, NC). An appropriate size arm cuff was placed on the right arm and patients were instructed to go about their usual activities, which consisted primarily of interviews with study investigators, imaging studies, and social/recreational activities designed for NIH inpatients. Recording was at 30-minute intervals from 0700 to 2200 hours and at 60-minute intervals overnight. These values were averaged for each subject.

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Statistics

Continuous data are expressed as mean ± standard deviation, and nominal data, as numbers and percent, or as otherwise noted. Comparisons between group means were made by 1-way ANOVA/ANCOVA with the Fisher protected least significant difference. Associations were tested by chi-square analysis or the Fisher exact test. Correlations were tested by regression analysis. All analyses were performed using StatView for Windows, version 5.0.1 (SAS Institute Inc., Cary, NC).

RESULTS

ECG Findings in TS Compared With 46,XX Age-Matched Controls

The average age of our cohort of 100 women with TS and 100 age-matched control women volunteers was 35 ± 11 years (range, 18–59 yr). Women with TS were 3 times more likely to have an abnormal ECG than controls (Table 1). Women with TS were significantly more likely to have left posterior fascicular block, T wave abnormalities, and accelerated AV conduction. There were no differences between the groups in findings of early or late transitional abnormality, right ventricular hypertrophy, low voltage, or atrial abnormalities (see Table 1). The average heart rate in women with TS (81 bpm; range, 50–114 bpm) was about 21% greater than that in controls (66 bpm; range, 40–93 bpm; $p < 0.0001$).

TABLE 1. Electrocardiogram (ECG) Findings in Turner Syndrome (TS)

ECG Finding	TS (n = 100)	Controls (n = 100)	OR (95% CI)	p Value
Left anterior fascicular block	5	1	5.2 (0.6–45.4)	0.212
Left posterior fascicular block	11	1	12.2 (1.5–96.7)	0.005
T wave	29	13	2.7 (1.3–5.6)	0.006
ST segment abnormality	1	0		>0.9999
Accelerated AV conduction	13	2	7.3 (1.6–33.4)	0.006
Early precordial transition	8	6	1.4 (0.5–4.1)	0.783
Late precordial transition	4	1	4.1 (0.5–37.6)	0.369
Poor R wave progression	6	8	0.7 (0.2–2.2)	0.783
Right ventricular hypertrophy	2	0		0.500
Left ventricular hypertrophy	1	0		>0.9999
Left atrial abnormality	1	1		>0.9999
Low voltage	2	3		>0.9999
Any of the above	55	30	2.9 (1.6–5.1)	0.0006

TABLE 2. ECG Intervals in TS and Controls

	TS (n = 100)	Controls (n = 100)	p Value*
PR† (ms)	136 ± 16	158 ± 18	< 0.0001
QRS† (ms)	86 ± 10	81 ± 7	0.0016
QT	370 ± 27	385 ± 29	< 0.0001
QTc† (ms)	424 ± 19	397 ± 18	< 0.0001
Heart rate (bpm)	81 ± 12	66 ± 11	< 0.0001

*Using ANCOVA, differences in PR, QRS, QT, and QTc intervals were tested taking into account age and heart rate as covariates. Difference in heart rate was tested taking into account age as covariate.

†Normal values for the PR are 120–200 ms, QRS < 100 ms, and QTc ≤ 440 ms.

There were marked differences in ECG intervals in women with TS compared to women without TS (Table 2 and Figure 1). The PR interval was significantly shorter, while the QRS was longer in women with TS. The QTc interval[1] was significantly longer in those with TS (423 ± 19 ms vs. 397 ± 18 ms; $p < 0.0001$). The distribution of QTc interval duration was shifted to the left in women with TS,

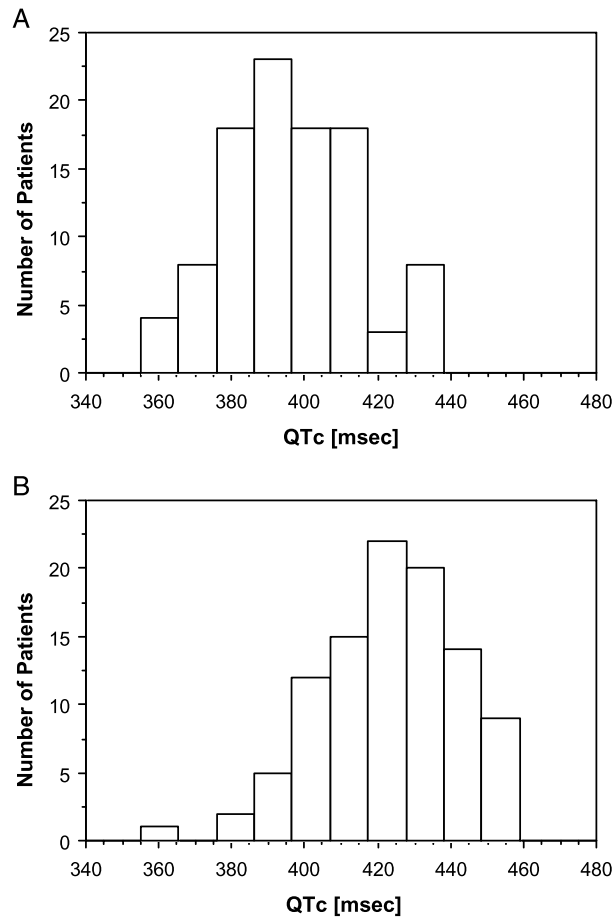

FIGURE 1. Frequency distribution of QTc interval duration in 100 women without TS (age-matched, 46,XX controls) (**A**) and 100 women with TS (**B**).

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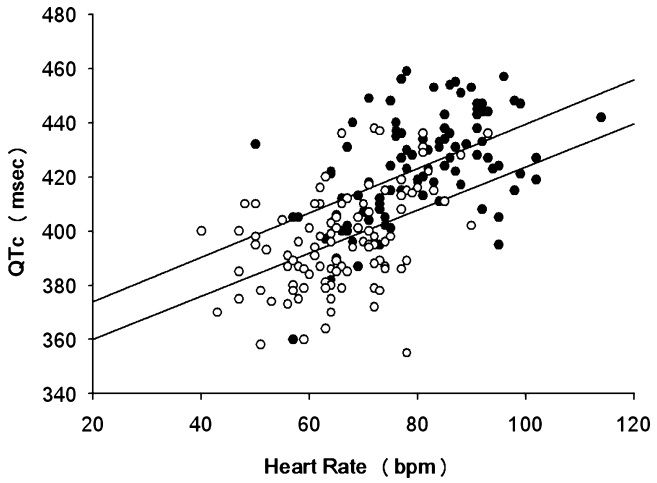

FIGURE 2. Heart rate and QTc length in women with TS (solid circles) and age-matched control women (open circles). Women with TS have a longer QTc interval compared with controls for every heart rate (ANCOVA: F-value for heart rate 59.16, $p < 0.0001$; F-value for TS vs. control 29.12, $p < 0.0001$.).

without evidence of bimodality (see Figure 1). Twenty-one women with TS (21%; 95% confidence interval, 12.5%–29.5%), but no controls had a prolonged QTc in the pathological range (>440 ms). The PR and QTc interval durations were not correlated in controls or the TS group. The QRS/QTc ratio was similar in the 2 groups: TS group = 0.204 ± 0.020; control group = 0.204 ± 0.024; p = 0.9.

To clarify the contribution of the heart rate to differences in interval duration in the 2 groups, we plotted heart rate compared with QTc for each group (Figure 2). While there was a strong positive correlation between heart rate and QTc in both groups, the QTc duration in TS was significantly higher for all rates (ANCOVA: F-value for heart rate 59.16, $p < 0.0001$; F-value for TS vs. control 29.12, $p < 0.0001$).

ECGs and Body Habitus in TS

We considered that short stature or other aspects of altered body habitus might contribute to ECG abnormalities in TS. However, height and body mass index were very similar in the groups with normal and abnormal ECGs (data not shown) and in groups with the shortest compared with the longest QTc duration (Table 3). Moreover, there was no correlation between height or body mass index and QTc (data not shown). Finally, chest dimensions determined by MR were not significantly different in the group with ECG abnormalities compared with that with normal ECGs (data not shown) or in short compared with long QTc tertiles (see Table 3).

Metabolic Factors and ECG Findings in TS

Metabolic factors including hyperglycemia, hyperlipidemia, and electrolyte or mineral abnormalities may contribute to ECG abnormalities and QTc prolongation, so we investigated these parameters with respect to ECG finding in TS. There were no significant differences in fasting glucose, lipid, K^+, Ca^{2+}, Mg^{2+} levels or thyroid function tests in the groups with normal compared with abnormal ECGs (data not shown), or between these parameters in tertiles with shortest compared with longest QTc (see Table 3).

Structural Anomalies of the Heart and Great Vessels and ECG Findings in TS

We investigated the relation between congenital anomalies of the cardiovascular system and the presence of ECG abnormalities. In this cohort of women with TS, 22% had bicuspid aortic valves, 11% had coarctation of the aorta, and 27% had either a bicuspid aortic valve, coarctation of the aorta, or both. There was no association between any combination of these anomalies and the presence of an abnormal ECG (Table 4). Additional congenital cardiovascular anomalies have been found in this population using MRA[13]. In this group, 49% had an elongated transverse aorta, 9% an aberrant right subclavian artery, 13% a persistent left superior vena cava, and 13% partial anomalous pulmonary venous return. There were no significant associations between the presence of any of these congenital structural anomalies and abnormal ECG findings.

To refine further the analysis, we grouped ECG abnormalities into predominantly left or right heart abnormalities to try to find some correlation with structural heart

TABLE 3. Characteristics of the Highest and Lower QTc Groups

	QTc Tertile (ms)		
	<417 (n = 34)	>432 (n = 34)	p Value
Age (yr)	35.0 ± 11.3	35.8 ± 11.5	0.8
Height (cm)	145.7 ± 7.7	146.1 ± 7.2	0.7
BMI (kg/m^2)	27.0 ± 6.6	28.4 ± 8.8	0.4
Thoracic dimension			
R-L (mm)	231.6 ± 13.4	230.5 ± 17.3	0.8
S-I (mm)	180.8 ± 20.4	178.8 ± 20.0	0.7
A-P (mm)	153.7 ± 12.6	154.5 ± 19.3	0.8
Volume (m^3)	0.013 ± 0.002	0.013 ± 0.003	0.8
Blood pressure			
Systolic (mm Hg)	112.9 ± 10.1	117.8 ± 12.1	0.08
Diastolic (mm Hg)	69.6 ± 8.0	72.9 ± 8.2	0.08
Metabolic factor			
Fasting glucose (mg/dL)	83.9 ± 11.0	87.3 ± 16.1	0.3
Cholesterol (mg/dL)	199.1 ± 34.5	211.4 ± 50.2	0.3
LDL-C (mg/dL)	127.0 ± 36.3	139.8 ± 51.9	0.2
HDL-C (mg/dL)	57.7 ± 15.0	56.7 ± 12.2	0.8
Triglycerides (mg/dL)	124.4 ± 80.5	129.2 ± 58.2	0.8
TSH (μIU/mL)	2.36 ± 1.63	2.26 ± 1.33	0.8
Potassium (mmol/L)	4.0 ± 0.3	3.9 ± 0.3	0.2
Calcium (mmol/L)	2.3 ± 0.1	2.3 ± 0.1	>0.9
Magnesium (mmol/L)	0.86 ± 0.08	0.86 ± 0.06	0.8

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TABLE 4. Congenital Cardiovascular Abnormalities and ECG Findings in TS

	No.	Normal ECG No. (%)	Abnormal ECG No. (%)	p Value
Congenital heart defect	40	20/40 (50)	20/40 (50)	0.67
Bicuspid aortic valve	22	10/22 (45)	12/22 (55)	>0.99
Coarctation	11	6/11 (55)	5/11 (45)	0.54
Bicuspid aortic valve ‖ coarctation	27	12/27 (44)	15/27 (56)	>0.99
Left superior vena cava	11	7/11 (64)	4/11 (36)	0.33
PAPVR	11	6/11 (55)	5/11 (45)	0.75
Elongated transverse aorta	40	23/40 (58)	17/40 (43)	0.08
Aberrant right subclavian artery	8	4/8 (50)	4/8 (50)	>0.99
Any of the above	58	30/58 (52)	28/58 (48)	0.26

Abbreviations: PAPVR = partial anomalous pulmonary venous return.

defects. Left heart abnormalities included left anterior fascicular block, precordial ST-T abnormalities, late precordial transition, poor R wave progression, LVH, and left atrial abnormality. Right heart abnormalities consisted of left posterior fascicular block, inferior ST-T abnormalities, early precordial transition, and right ventricular hypertrophy. However, no trends or correlations with left- or right-sided ECG abnormalities and congenital heart defects were detected. Finally, QTc duration was similar in those with and without confirmed congenital heart defects (data not shown).

Blood Pressure and ECG Findings in TS

Hypertension and LVH may cause ECG abnormalities, including ST and T wave changes and QT prolongation. However, there were no differences in average systolic or diastolic pressures in our TS groups with normal compared with abnormal ECGs (data not shown) or between lowest compared with highest QTc tertiles (see Table 3). Nor were LV dimensions, determined by echocardiogram, significantly different in the lowest and highest QTc tertiles (Table 5), although there was a trend toward greater LVM corrected for height in the long QTc group ($p = 0.08$).

TABLE 5. QTc and Left Ventricular Echocardiographic Parameters in TS

	QTc (ms)		
Parameter	<417 (n = 34)	>432 (n = 34)	p Value
Ventricular septal thickness (mm)	7.4 ± 0.9	7.8 ± 1.2	0.2
Posterior wall thickness (mm)	7.2 ± 9	7.6 ± 1.2	0.2
LV internal-diastolic dimension (mm)	42.8 ± 3.3	42.3 ± 5.0	0.6
LV internal-systolic dimension (mm)	26.3 ± 2.7	26.6 ± 4.1	0.6
LV mass (g)	94.8 ± 14.6	101.7 ± 32.9	0.3
LV mass/BSA (g/m^2)	63 ± 10	68 ± 18	0.2
LV mass/height ($g/m^{2.7}$)	33 ± 5	37 ± 11	0.08

Chronologic Age and ECG Findings in TS and 46,XX Age-Matched Controls

Chronologic age was similar in women with TS and normal ECGs compared with women with abnormal tracings (35 ± 11 vs. 36 ± 11 yr; $p = 0.8$) and in women with shortest compared with longest QTc tertiles (see Table 3). The QTc interval normally increases with age, as seen in our control population, but not in the women with TS (Figure 3).

Medications and QTc in Women With TS

Ten women were on medications that may rarely be associated with QTc prolongation (for example, lithium, fexofenadine, esomeprazole, citalopram, fluoxetine, doxepin)[21,36]. Of these, only 2 had a QTc >440 ms. Eliminating these 10 women from the analysis did not change the results (423 ± 20 vs. 397 ± 18 ms; $p < 0.0001$).

DISCUSSION

The ECG is an important screening tool for the detection of underlying heart disease. Aberrant myocardial depolarization (QRS complex) or repolarization (QT interval) most commonly reflects ischemic heart disease, LVH, or cardiomyopathy. The current study has documented the presence of previously unrecognized conduction and repolarization abnormalities revealed on electrocardiography in women with TS. We have found that left posterior fascicular block, T wave abnormalities, accelerated AV conduction and QTc prolongation are common in women with TS, independent from the well-known congenital anatomical defects associated with the syndrome. These abnormal findings were not explained by small stature, abnormal chest architecture, or metabolic disorder in women with TS. Finally, LVH and ischemic heart disease appear to be unlikely causes of the ECG abnormalities in this relatively young group of women. Thus, it appears that cardiac conduction and repolarization abnormalities are intrinsic features of TS.

The fact that women with TS as a group have significantly longer QTc intervals compared with age-matched controls is an unexpected and potentially clinically significant finding. Twenty-one percent of women with TS

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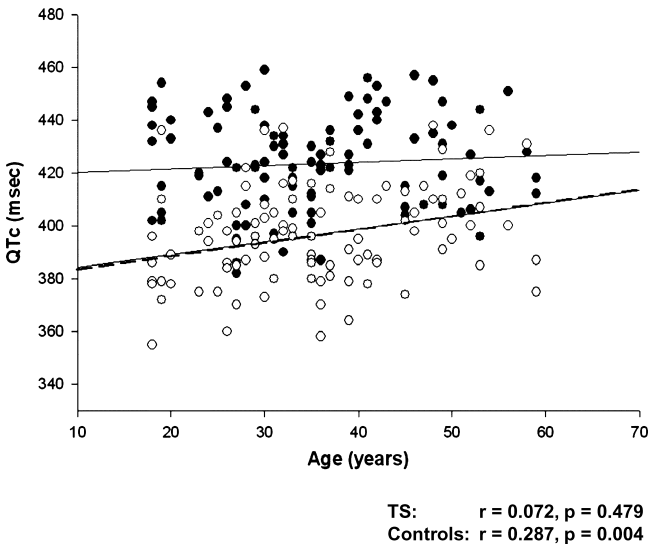

FIGURE 3. QTc increases with age in control women (open circles) but not in women with TS (solid circles). The QTc interval duration is plotted against age for 100 women with TS and 100 age-matched control women.

had a QTc >440 ms, but not one of the control women did. Prolongation of this interval >440 ms may be associated with increased risk for cardiac arrhythmias and sudden death[22]. Congenital long QT syndromes are caused by mutations/deletions of genes encoding ion channel components[16]. Acquired long QT syndromes may be caused by drugs, ischemic or hypertrophic heart disease, and autonomic neuropathy[16]. Drugs are obviously not the cause of QTc prolongation in our TS study group.

QTc prolongation has been associated with ischemic or hypertrophic heart disease in older populations with clinically obvious coronary disease and hypertension. Women with TS have increased risk for coronary disease and hypertension[6,10,12,14,23], but these diseases were not common in our relatively young study population. Only 1 woman with TS had LVH by ECG. Moreover, LVM was not correlated with QTc duration in our study subjects, although LVM normalized to height showed a trend in that direction. The average blood pressure in the long QTc tertile was well within the normal range (see Table 3). QTc duration normally increases with age[3,19,35] as seen in our control group. There was, however, no relation between age and QTc duration in the TS group, suggesting that this prolongation reflects a congenital aspect of the syndrome. The X chromosome includes genes encoding proteins implicated in membrane repolarization. For example, KCNE1-like (KCNE1L; Xq22.3) encodes a 142-amino-acid peptide with homology to KCNE1 (minK), a protein associated with the KCNQ1 potassium channel (KVLQT1)[28]. Mutations/deletions of either of these genes may cause the ''long QT syndrome''[30]. Women with TS also demonstrate faster heart rates and accelerated AV conduction, compared with controls. Autonomic dysregulation might contribute to these phenomena in patients with TS. For example, excessive sympathetic drive or responsiveness could explain the higher heart rate and accelerated AV conduction as well as QTc prolongation in TS[15,27].

Several studies have reported an association between the length of the QTc interval and mortality[3,8,17,25,31]. In such epidemiologic studies, it is difficult to separate the effect of independent cardiovascular risk factors, such as age, dyslipidemia, diabetes, hypertension, obesity, and known ischemic heart disease, that typically characterize the groups with longer QTc duration, from the predictive value of a prolonged QTc in the absence of these established risk factors—such as our group with TS. Whether a prolonged QTc is associated with early mortality or sudden cardiac death in TS is uncertain. Although women with TS are not known to experience high rates of sudden death or arrhythmias, this may be because investigators have not looked for these conditions among a small and scattered population. Women with TS apparently are at increased risk of cardiac mortality[10,12,20], so further investigation to determine the underlying cause and consequences of this prolonged QTc interval is warranted. Moreover, given that more than 20% of women with TS have QTc durations in the pathological range, it is probably wise to monitor ECGs in patients with TS when prescribing drugs associated with QTc prolongation.

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