Original Article

MEDICAL CARE OF GIRLS WITH TURNER SYNDROME: WHERE ARE WE LACKING?

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ABSTRACT

Objective: To characterize the medical care of a large cohort of girls with Turner syndrome with a focus on changes in management since establishment of international consensus guidelines in 2007.

Methods: We reviewed medical records of patients followed up for Turner syndrome between 2000 and 2010.

Results: A total of 128 girls aged 13.2 ± 0.5 years were identified. Average age at diagnosis was 4.1 ± 5.1 years. Overall, medical assessments performed included a hearing test in 56%, thyroid screening in 95%, renal ultrasonography in 100%, and echocardiography in 100%. Before 2007, none of the patients had screening performed for celiac disease, dyslipidemia, or liver dysfunction, and none had routine electrocardiography or cardiac magnetic resonance imaging. Since 2007, 63% were screened for celiac disease, 54% for liver abnormalities, and 38% for dyslipidemia. Electrocardiography was performed in 23%, while cardiac magnetic resonance imaging was performed in 39%. Although conjugated equine oral estrogen was the main mode of estrogen replacement, a significant increase was noted in the use of transdermal estrogen during the past 2 years compared with that observed in the earlier interval (78% vs 10%, respectively).

Conclusions: Although changes in medical practice have occurred since establishment of the international Turner syndrome guidelines, screening for associated comorbidities was deficient in greater than 50% of the patients in our study. This is the first study evaluating medical care in a large cohort of pediatric patients with Turner syndrome, and our findings emphasize the need for continual education of all physicians involved in the care of this population. **(Endocr Pract. 2011;17:747-752)**

Abbreviations:
BMI = body mass index; **ECG =** electrocardiogram; **GH** = growth hormone; **MRA** = magnetic resonance angiography; **MRI** = magnetic resonance imaging; **TS** = Turner syndrome

INTRODUCTION

Turner syndrome (TS) is a disorder in females characterized by complete or partial absence of an X chromosome in association with typical phenotypic features (1,2). Although short stature and ovarian failure are the most prominent characteristics, affected girls have a wide range of medical problems including cardiac, renal, otologic, skeletal, and metabolic issues. In addition, women with TS have decreased life expectancy due to associated comorbidities, necessitating lifelong follow-up and screening (3,4). In 2007, international consensus guidelines were published regarding care of girls and women with TS (5). To what extent these recommendations have resulted in a change in the medical care of young girls and adolescents with TS is unknown. However, data published on the care of more than 500 patients with TS in adulthood indicate that only 3.5% currently undergo the medical follow-up recommended in the 2007 consensus guidelines (6).

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Although the diagnosis of TS in childhood usually results in intensive medical evaluation and follow-up, most of the care is focused on management of short stature and ovarian failure (5,7). Studies regarding adequacy of screening and ongoing monitoring for other associated comorbidities in children are scarce. In one study investigating screening at diagnosis based on the initial TS guidelines published in 1994, 34%, 30%, and 73% of girls were not evaluated for cardiac, renal, and hearing problems, respectively, despite being under the care of an endocrinologist (8,9). In another small study, 79% of affected girls underwent these screening tests, whereas only 36% of affected adults had been adequately evaluated (10). Thus, while recommended care appears to be implemented more often in children with TS than in adult women with TS, medical care in children is still not optimal. To date, no other data are available on adequacy of screening for other comorbidities and ongoing surveillance in children with TS. Thus, the objective of this study was to characterize the medical care and prevalence of comorbidities in a large cohort of girls with TS followed up in a pediatric endocrinology clinic with a focus on changes in management since 2007.

METHODS

After institutional review board approval, medical records of girls followed up for TS in the endocrine clinic at Riley Hospital for Children in Indianapolis, Indiana, between 2000 and 2010 were identified. Data collected at initial visit included age at diagnosis, karyotype, phenotypic features, cardiac evaluation, renal evaluation, hearing evaluation, and reason for referral to the endocrine clinic. Additional data collected included age, body mass index (BMI), and height at the last visit. The frequency of screening evaluations for the following conditions were assessed: celiac disease, thyroid problems, diabetes, dyslipidemia, hypertension, liver disease, scoliosis, cardiac abnormalities (magnetic resonance imaging [MRI] and electrocardiogram [ECG]), and behavioral problems. Growth data collected included age at initiation of growth hormone (GH) therapy, duration of GH therapy, final adult height, and midparental height when available. Data obtained on ovarian function included history of spontaneous puberty, ovarian failure, age at onset of pubertal induction, estrogen replacement regimen, and duration to cycling. The 2007 recommendations for laboratory testing, hearing evaluations, and cardiac monitoring are presented and contrasted with the results pertaining to these aspects of clinical management in our patients.

Statistical Analysis

The descriptive statistics of the sample and the outcome measures were calculated. Data are expressed as mean ± standard deviation. BMI percentiles were derived using a Web-based BMI calculator based on the 2000 growth charts of the Centers for Disease Control and Prevention, National Center for Health Statistics, Atlanta, Georgia (11). All calculations were performed using the SPSS software version 16.0 (SPSS, Chicago, Illinois) or Microsoft Excel 2007 (for descriptive statistics). The α level was set at 0.05.

RESULTS

Of 131 girls identified, 128 aged 13.2 ± 0.5 years had complete medical records and were included in the analysis. The average age at diagnosis was 4.1 ± 5.1 years (range, birth-16.33 years). In 64 girls (50%), TS was diagnosed at birth because of dysmorphic features (cystic hygroma, lymphedema, or webbing of the neck), whereas in the other 50%, TS was diagnosed at an average age of 9.3 ± 3.7 years because of short stature and/or primary amenorrhea. A 45,X karyotype was found in 58% of patients. At diagnosis, 37% had cardiac anomalies, 32% had renal anomalies, and 38% had lymphedema. Medical assessments performed at diagnosis included a hearing test in 56%, thyroid screening in 95% (age ≥4 years), blood pressure measurement in 100%, renal ultrasonography in 100%, and echocardiography in 100%. A summary of baseline patient characteristics is provided in Table 1.

Trends in Screening Since 2007 and Ongoing Monitoring

Guidelines for Laboratory Testing (5):

- Celiac disease (older than 4 years): at diagnosis, then every 2 to 5 years
- Liver, lipids, and fasting blood glucose (older than 10 years): at diagnosis, then annually
- Thyroid function tests (4 years or older): at diagnosis, then annually

Before 2007, none of the patients had celiac, liver, lipid, or fasting blood glucose screens done. Since 2007, 63% of girls were tested for celiac disease (of whom 5% had elevated tissue transglutaminase antibodies requiring endoscopy), 54% had liver screening (of whom 13% had major elevations in liver transaminases requiring referral to gastroenterology), 38% had lipid levels measured (of whom 26% had an abnormal lipid profile [total cholesterol >200 mg/dL, triglycerides >150 mg/dL, or both]), and 58% had fasting blood glucose measured routinely. Type 1 diabetes mellitus was diagnosed in 2 of 58 girls who were screened for diabetes (3%) and they were maintained on insulin therapy. Annual thyroid testing was done on all girls 4 years or older. No changes in patterns for screening for thyroid abnormalities were observed in the past 10 years. Hashimoto thyroiditis was noted in 36 patients (30%), while Graves disease was diagnosed in 2 patients (2%). An additional 2 girls (2%) had a history of congenital hypothyroidism.

Table 1
Baseline Characteristics and Assessments in 128 Girls With Turner Syndrome

Characteristics and assessments	Patient population (n = 128)
Karyotype, No. (%)	
45,X	74 (58)
Mosaic	54 (42)
Structural abnormalities	1 (1)
Echocardiography findings, No. (%)	
Normal	80 (63)
Bicuspid aortic valve	31 (24)
Coarctation of the aorta	13 (10)
Other (atrial septal defect, ventricular septal defect, aortic dilatation, partial anomalous pulmonary venous return)	4 (3)
Hypertension, No. (%)	14 (11)
Renal ultrasonography findings, No. (%)	
Normal	87 (68)
Horseshoe kidney	23 (18)
Ureteropelvic junction obstruction	5 (4)
Other (duplicated collecting system, vesicoureteral reflux grades II-III, single kidney, malrotation)	13 (10)
Hearing screening findings, No. (%)	
Normal	79 (62)
Conductive hearing loss	24 (19)
Sensorineural hearing loss	22 (17)
Unspecified	3 (2)
Scoliosis of 8-35 degrees, No. (%)	13 (10)
Other comorbidities	
Behavioral problems (attention deficit hyperactivity disorder, autism, anxiety, depression)	36 (28)
Inflammatory bowel disease	2 (2)

Hearing Evaluation

- Guidelines (5): At diagnosis, then ears, nose, and throat evaluation and audiologic evaluation every 1 to 5 years

Hearing problems were noted in 38% of the 72 patients screened. These problems included bilateral and unilateral conductive hearing loss, as well as bilateral sensorineural hearing loss. Patients with known hearing abnormalities were followed up with regular ear, nose, and throat evaluations. However, of the patients noted to have normal hearing screens at diagnosis, none underwent repeated assessments as recommended.

Cardiac Monitoring

- Guidelines (5): At diagnosis, ECG and echocardiography (infants and young girls) or MRI and echocardiography (older girls); monitoring: imaging every 5 to 10 years if normal anatomy, MRI in all girls old enough to tolerate the procedure if they have only had echocardiography

Before 2007, none of the patients underwent ECG either at diagnosis or for routine screening. Since 2007, ECG was done in 30 patients (23%), of whom 11 (37%) were noted to have abnormalities including prolonged QT, nonspecific T- and ST-wave changes, conduction delay, and

supraventricular tachycardia. Although 100% underwent echocardiography at diagnosis, only patients with documented cardiac anomalies received repeated cardiac surveillance on the basis of the guidelines. This practice pattern had not changed since 2007. In contrast, cardiac MRI and magnetic resonance angiography (MRA) was done in 39% of patients since 2007. Abnormalities noted on MRI included mild-to-moderate aortic root and ascending aortic dilatation, elongation of transverse aortic arch, and structural anomalies of the superior vena cava. These findings were not detected on routine echocardiography. Only 2 of 18 girls between the ages of 5 and 10 years had cardiac MRI performed. One had normal study findings and the other was noted to have elongation of the transverse aortic arch with mild-to-moderate aortic root dilatation. Blood pressure was monitored annually in all patients, of whom 11% were noted to have hypertension requiring treatment. There were no changes in screening for blood pressure problems since 2007. Details of the medical assessments performed during the study interval are summarized in Table 2.

Ovarian Function and Estrogen Replacement

- Guidelines (5): Although there is no consensus regarding the optimal form and route used for estrogen replacement therapy, it is suggested that the timing should mimic physiologic pubertal development as much as possible.

Premature ovarian failure was present in 111 patients (87%). Fifteen of these girls (13%) developed transient breast development, but went on to require hormone replacement therapy to complete puberty and initiate menarche, whereas 4 girls (4%) had spontaneous puberty and regular menses. During the 10 years of the study, 72 patients with ovarian failure (65%) received estrogen replacement therapy. The average age of estrogen replacement was 13.96 ± 1.55 years, and the average duration to cycling was 1.98 ± 0.65 years. Conjugated equine oral estrogen was the main mode of estrogen replacement, having been prescribed in 90% of girls treated before 2007. However, since 2007 there was a significant increase in the use of transdermal estrogen, with 25 girls (78%) receiving estrogen by this modality vs only 5 girls (22%) receiving oral estrogen. The age at initiation of estrogen replacement therapy since 2007 was unchanged compared with the age at initiation in the previous interval (14.01 ± 1.47 vs 13.7 ± 1.75; $P = .57$). Among 12 endocrinologists practicing at our institution, 13 different estrogen regimens were used.

Growth and BMI Data

The average age at initiation of GH treatment was 7.9 ± 4.07 years (range, 0.66-15.58 years). GH therapy was discussed with all patients, 3 of whom declined therapy. Among patients who achieved final adult height, the average duration of GH therapy was 5.7 ± 2.9 years (range, 1-12.16 years). Adverse effects from treatment included

Table 2
Medical Assessments Performed in Girls With Turner Syndrome

Assessments (No. of patients eligible for screening based on published guidelines)	No. (%) of patients actually screened	Patients with abnormal findings, No. (%)
Celiac disease screening (n = 121)[a]	77 (63)	4 (5)
Liver enzyme screening (n = 99)[b]	54 (54)	7 (13)
Lipid levels (n = 99)[b]	38 (38)	10 (26)
Blood glucose (n = 99)[b]	58 (58)	2 (3)
Thyroid function (n = 121)[a]	121 (100)	38 (31)
Audiometry (n = 128)[c]	72 (56)	28 (39)
Electrocardiography (n = 128)[c]	30 (23)	11 (37)
Cardiac magnetic resonance imaging (n = 99)[b]	39 (39)	10 (26)[d]

[a] Number of patients screened for celiac disease and thyroid function included all girls aged 4 years and older.
[b] Number of patients screened for liver function, dyslipidemia, glucose levels, and cardiac abnormalities on magnetic resonance imaging included girls aged 10 years and older.
[c] Number of patients screened by audiometry and electrocardiography included all study patients.
[d] The percentage of patients with abnormal magnetic resonance imaging represents the percentage of patients with abnormal magnetic resonance imaging findings not detected by routine echocardiography.

slipped capital femoral epiphysis in 3 patients and pseudotumor cerebri in 1 patient. Of the 128 girls, 54 (42%) had achieved final adult height at the time of this review. Average final adult height was 151.3 ± 5.6 cm (–1.83 standard deviation score). Average midparental height – final adult height was 13.08 ± 5.9 cm. At the last visit, 61 (48%) had a BMI greater than the 85th percentile, of whom 39 (64%) were clinically obese (BMI >95th percentile).

DISCUSSION

This is the first study evaluating medical care in a large cohort of pediatric patients with TS. While changes in medical practice have occurred since establishment of the international TS guidelines (5), recommended surveillance for associated conditions was deficient in greater than 50% of our patients. Despite this, significant changes since publication of the guidelines were identified in some areas. Before 2007, none of these patients were screened for celiac disease, dyslipidemia, liver dysfunction, or blood glucose levels, whereas 38% to 63% of the cohort was evaluated appropriately for these problems in the years since. In contrast, rates of hearing assessments were relatively poor in our study, similar to what has been observed in adults, regardless of the known increased risk of hearing problems and sensorineural hearing loss in the TS population (12,13).

Cardiac surveillance in our study was also suboptimal. Although echocardiography was done at diagnosis in 100% of patients, which is much higher than what has been reported by others (9,10), ECG and cardiac MRI and MRA screening were performed in only 23% and 39%, respectively, since 2007. Given that mortality in women with TS is 3-fold higher than in the general population, with cardiac problems accounting for 41% of all deaths (14), our data support the need for improved cardiac surveillance even in younger patients.

The most dramatic change in management since 2007 was a marked increase in the use of transdermal vs oral conjugated estrogen for puberty induction, reflecting a general view that this is a more physiologic and favorable mode of estrogen replacement. In the United States, conjugated oral equine estrogens have historically been the most widely used form of estrogen for the induction of puberty in girls with TS (15). However, transdermal estrogen is steadily gaining in popularity. In 1 uncontrolled study of 15 hypogonadal girls, 8 of whom had TS, nocturnal, low-dosage transdermal estrogen resulted in physiologic estradiol concentrations and breast development within 3 to 6 months (16). In another study of 12 girls with TS, transdermal estrogen resulted in better uterine growth and bone accrual at the level of the spine than oral estrogen after 1 year of treatment (17). Thus, the change in practice noted is consistent with the most recent literature on estrogen replacement. Interestingly, however, in our study, the average age of pubertal induction and time to menses did not change throughout the 10 years of analysis despite recommendations to start puberty at a more physiologic age of 11 to 12 years for greater concordance with peers.

Finally, the prevalence of comorbidities (cardiac, renal, hearing, and thyroid problems) in the girls with TS in our study is similar to what has been reported elsewhere (12,18-20). However, the incidence of cardiac anomalies on MRI/MRA (particularly partial anomalous pulmonary venous return) was not as high as previously reported. In our study, partial anomalous pulmonary venous return was noted in 1 of 39 patients (3%), compared with the incidence of 13% reported by Ho et al (21). This could be related to the relatively small number of patients (n = 39) who underwent cardiac MRI in our study. Another important finding is the increased incidence of abnormalities (36%) noted on ECG despite the relatively small number of patients screened. Although studies regarding prevalence of ECG abnormalities in young girls and adolescents with TS are scarce, a study of 78 girls with TS (aged 7-17 years) found an increased prevalence of conduction abnormalities, T-wave changes, and QT prolongations similar to our findings (22).

Our study has limitations because of its retrospective design. It also represents data from only 1 center, which could affect its generalizability. Our section has 12 board-certified pediatric endocrinologists with different training backgrounds. We also have a pediatric radiologist and pediatric cardiologist with special expertise in the field of cardiac MRI in children. Thus, the clinical practice followed at our institution probably ranks among the highest in the nation in this area, and our results could overestimate the overall general adherence to the consensus guidelines.

The reasons behind failure of compliance with the international consensus guidelines is unclear and likely multifactorial. A general lack of awareness and comfort with established practice habits were probably contributing factors. The fact that some guidelines represent expert opinion rather than being evidence-based may engender skepticism on the part of some practitioners regarding the need to comply with them. Only time will tell if adherence rates will change as results from additional studies providing evidence-based support for these recommendations filter down into the clinical setting.

CONCLUSION

Our findings emphasize the need for continuous education for all medical providers involved in the care of girls with TS. Given the high rates of related morbidities, special emphasis should be placed on routine screening for hearing problems, dyslipidemia, liver disease, and cardiac health (MRI and ECG), particularly in older girls. Patient education and initiation of early screenings during childhood might also improve overall adherence to recommended

care as those girls transition from the pediatric to the adult world. Collaborative efforts between primary care physicians and subspecialists are needed to improve the diagnosis, screening, and follow-up of all girls and women with TS.

DISCLOSURE

Dr. Eugster participates in an Eli Lilly–sponsored natural history study of girls with TS. Dr. Nabhan has no multiplicity of interest to disclose.

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