Approach to the Patient with Turner Syndrome

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Upon completion of this educational activity, participants should be able to
- Address cardiac, growth, gonadal and developmental abnormalities in patients with Turner syndrome.
- Implement recommended health care screening tests for patients with Turner syndrome

Target Audience
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Turner syndrome (TS) occurs in about 1:4000 live births and describes females with a broad constellation of problems associated with loss of an entire sex chromosome or a portion of the X chromosome containing the tip of its short arm. TS is associated with an astounding array of potential abnormalities, most of them thought to be caused by haploinsufficiency of genes that are normally expressed by both X chromosomes. A health care checklist is provided that suggests screening tests at specific ages and intervals for problems such as strabismus, hearing loss, and autoimmune thyroid disease. Four areas of major concern in TS are discussed: growth failure, cardiovascular disease, gonadal failure, and learning disabilities. GH therapy should generally begin as soon as growth failure occurs, allowing for rapid normalization of height. Cardiac imaging, preferably magnetic resonance imaging, should be performed at diagnosis and repeated at 5- to 10-yr intervals to assess for congenital heart abnormalities and the emergence of aortic dilatation, a precursor to aortic dissection. Hypertension should be aggressively treated. For those with gonadal dysgenesis, hormonal replacement therapy should begin at a normal pubertal age and be continued until the age of 50 yr. Transdermal estradiol provides the most physiological replacement. Finally, nonverbal learning disabilities marked by deficits in visual-spatial-organizational skills, complex psychomotor skills, and social skills are common in TS. Neuropsychological testing should be routine and families given support in obtaining appropriate therapy, including special accommodations at school. (***J Clin Endocrinol Metab*** **95: 1487–1495, 2010)**

The Case

An 11.5-yr-old girl, K.S., was found to have 45,X Turner syndrome (TS) during a work-up for short stature. She was full term with a weight of 3.5 kg (0.21 SD) and length of 50.8 cm (0.59 SD). Her parents report thickened hands and feet, difficulty feeding, and gastroesophageal reflux. Her weight fell to the sixth percentile (−1.52 SD) and her length to the 24th percentile (−0.90 SD) by 8 months. She received speech therapy for feeding and, later, articulation problems. She had chronic otitis media requiring pressure-equalizing tube surgery four times and an adenoidectomy

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Abbreviations: BMD, Bone mineral density; BP, blood pressure; CEE, conjugated equine estrogen; HCP, health care provider; HRT, hormone replacement therapy; MRI, magnetic resonance imaging; NLD, nonverbal learning disability; PAPVR, partial anomalous pulmonary venous return; QOL, quality of life; SDS, SD score; SHOX, short-stature homeobox-containing gene on the X chromosome; TDE, transdermal estradiol; TS, Turner syndrome; TSS, Turner Syndrome Society.

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and had recently been noted to have a mild unilateral sensorineural hearing deficit. The patient worked hard in school but had problems with handwriting and written output, completing work on time, and social interactions. She was on no medications. On physical examination, she had a body mass index of 19.3 kg/m^2 and a height at the 10th percentile (−1.27 SD), well below her midparental target height at the 90th percentile (1.5 SD). Findings consistent with TS included abnormal auricles, high palate with broad lateral palatal ridges, retrognathia, short fourth metacarpals, nail dysplasia, multiple nevi, moderate lymphedema of left foot and lower leg, flat feet, Tanner I breasts, and Tanner II pubic hair. A cardiac magnetic resonance imaging (MRI) revealed partial anomalous pulmonary venous return (PAPVR). A renal ultrasound and routine laboratory screening tests were normal except for elevated FSH and LH levels.

This case will be used to illustrate the range of problems associated with TS, their presumed etiologies, and some of the newer recommendations and controversies in care. Specific issues to be addressed include use of MRI to screen for cardiac anomalies, early initiation of GH therapy, initiation of hormone replacement therapy (HRT) at the time of normal puberty, and referral for developmental/ neurocognitive evaluations at the time of diagnosis.

Background

One of the X chromosomes is silenced in the somatic cells of normal females early in development to achieve some degree of dosage compensation between males and females because the X chromosome contains many genes (>1000), whereas the Y chromosome has relatively few genes (~200). However, 15–25% of genes on the inactive X continue to be expressed. Many of these so-called pseudoautosomal genes have homologous genes on the Y chromosome and are clustered on the tip of the X short arm (1).

TS defines females who have lost an entire sex chromosome or a portion of the X chromosome that includes the tip of its short arm and who have one or more problems commonly associated with TS such as short stature or gonadal insufficiency. In a routine TS clinic, about half of the individuals have a 45,X karyotype and 20–30% has mosaicism (45,X plus at least one other cell line), whereas the remainder has structural abnormalities (2).

Haploinsufficiency of short-stature homeobox-containing gene on the X chromosome (SHOX)

Short stature, the most common physical finding in TS is caused in large part by haploinsufficiency of the SHOX expression in chondrocytes. SHOX (3) belongs to a family of homeobox genes, transcriptional regulators and key controllers of developmental processes. Localization of SHOX expression during embryogenesis correlates with many specific skeletal anomalies such as cubitus valgus, genu valgum, and short fourth metacarpals (Table 1). SHOX is localized within the first and second pharyngeal arches of the embryo from 6 wk gestation onward (4). These arches develop into the maxilla, mandible, and ossicles of the middle ear; muscles involved in opening the eustachian tube, dampening sounds, chewing, modulating tension of the soft palate, and changing facial expressions; and most of the tongue and outer ear. Therefore, haploinsufficiency of SHOX expression in patients such as K.S. likely explains features such as a high palate, prominent ears, chronic otitis media, obstructive sleep apnea, increased sensitivity to noise, and problems learning how to suck, blow, eat, and articulate.

Haploinsufficiency of a lymphatic gene

Haploinsufficiency of a pseudoautosomal gene has been postulated to cause maldevelopment of the lymphatics. Absence or hypoplasia of lymphatics causes generalized lymphedema, and a cystic hygroma may be formed by accumulation of fluid in the connective tissue of the neck (5), leaving a low upward-sweeping posterior hairline, webbed neck, nail dysplasia (deeply set, narrow nails), and lymphedematous hands and feet at birth (Table 1). Lymphedema is generally identified at birth and gradually improves, but in some individuals such as K.S., it may first become apparent at an older age.

Haploinsufficiency of genes involved in ovarian function

Haploinsufficiency of multiple genes on both arms of the X chromosome (both X chromosomes remain active in germ cells), in addition to pairing failure during meiosis, cause gonadal dysgenesis in TS. Germ cell development is normal in TS, but there is accelerated loss of oocytes by 15 wk gestation (6).

Other problems common to TS are likely caused by X-linked disorders, imprinting, and haploinsufficiency of other genes.

Diagnosis

Diagnosis of TS requires a standard 30-cell karyotype. In a routine TS clinic, roughly half has a 45,X karyotype, 20–30% has mosaicism (45,X plus at least one other cell line), and the remainder has structural abnormalities. The phenotype of TS is extraordinarily broad. Individuals with a 45,X karyotype (often the result of losing a structurally abnormal sex chromo-

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TABLE 1. Clinical features of TS by frequency and etiology

	Haploinsufficiency of genes on the X chromosome				
	SHOX		Putative	Germ cell survival	
Frequency	Physical	Medical	lymphatic gene	genes	Other/unknown
Greater than 50%	Short stature Prominent ears Retrognathia Narrow palate	Growth failure Chronic otitis media Low BMD Fractures	Low posterior hairline Lymphedema Nail dysplasia	Infertility Gonadal failure Delayed puberty	Learning disability Unfavorable body composition
25–50%	Cubitus valgus Short fourth metacarpals Ptosis[a] Strabismus[a]	Feeding problem Sensorineural hearing loss[a]	Webbed neck		Renal malformation Hypertension Multiple nevi
10–25%	Epicanthal folds[a] Scoliosis Kyphosis Pectus excavatum Flat feet	Obstructive sleep apnea Articulation problems	Single palmar crease Inverted nipples[a]		Hypothyroidism Aortic coarctation Bicuspid aortic valve Increased liver enzymes Diabetes mellitus
Less than 10%	Genu valgum Madelung deformity Patellar dislocation	Hyperacusis			Celiac disease Inflammatory bowel disease von Willebrand's disease JRA Pilomatrixoma Aortic dissection Prolonged QT

JRA, Juvenile rheumatoid arthritis.

[a] Relationship to haploinsufficiency not well established.

some) tend to have a more severe phenotype than those who are mosaic with a normal cell line (45,X/46,XX or 45,X/46,XY). However, there is no predictable phenotype-genotype correlation. The Y chromosome confers an increased risk for gonadoblastoma and subsequent germ cell tumor formation (7), probably related to the presence of the specific protein-Y encoded gene located near the centromere. Individuals with Y material on karyotype should generally undergo laparoscopic gonadectomies; however, because some have had spontaneous pregnancies, close observation alone seems reasonable for those without evidence of gonadal insufficiency. Tumors have been found in a few patients with Y material detected by PCR or fluorescent *in situ* hybridization alone (8); however, it is not clear whether these methodologies should be routinely used.

Except for those diagnosed at birth for lymphedema and webbed neck, most postnatal diagnoses are delayed for years (2), with 38% being diagnosed in adulthood (9). In K.S.'s case, TS should have been considered in infancy, given her failure to thrive. Although her height never fell below the fifth percentile, she was moving away from her target height at the 90th percentile.

Therapeutic strategies

TS is associated with an astounding array of potential abnormalities (Table 1), making it a challenging disorder for health care providers (HCPs) and families. If possible, patients/families with TS such as K.S. should be treated in a multidisciplinary center experienced in their care. All families are encouraged to network with others through groups such as the Turner Syndrome Society (TSS), tsparents-3@yahoogroups.com, and TS camps. Support groups such as ts-pregnancy@yahoogroups.com also exist for parents with a prenatal diagnosis of TS. Written guidelines for HCPs, such as Care of Girls and Women with Turner Syndrome Guideline of the Turner Syndrome Study Group (10) and condensed summaries for HCPs and families (Table 2), help them to anticipate problems and appointments.

Growth failure

Growth failure is a problem for virtually all individuals with TS, with untreated individuals achieving an average adult stature 20 cm shorter than that of their peers. Growth failure generally begins *in utero*, continues into infancy and childhood, and is accentuated by the absence

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TABLE 2. Health care checklist for individuals with TS[a]

Problems	Screening test/referral	Timing of Tests			
		At Dx	Q visit	Q year	Other
Hip dislocation	Physical examination (including height, weight, BP, and calculation of BMI)	X	In infancy		
Feeding problems		X	In Infancy		
Strabismus		X	4 months to 5 yr		
Otitis media		X	All childhood		
Growth failure		X	All childhood		
Pubertal delay		X	Adolescence		
Scoliosis/kyphosis		X	While growing		
Dysplastic nevi		X	School-age on		
Lymphedema		X	Lifelong		
Hypertension		X	Lifelong		
Needs information/support	Refer to TSS, other support groups	X			
Structural renal abnormalities	Renal ultrasound	X			
Cardiac abnormality[b]	Examination by cardiologist; EKG; MRI/echo	X			Q 5–10 yr
Conductive and SNHL	Formal audiology exam	X			Q 1–3 yr
Gonadal dysfunction	FSH, LH	X			At ages 0.5–3 and 10–12 yr
Strabismus and hyperopia	Formal eye examination	X			At 1–1.5 yr
Celiac disease	Serum IgA, TTG IgA Ab	X			Q 2–5 yr (begin about age 4 yr)
Autoimmune thyroid disease	T_4, TSH	X		Begin about age 4 yr	
Developmental, educational, social problems	Developmental, educational, and/or psychosocial examination	X			Before school entry
Palatal/occlusive abnormalities	Orthodontic evaluation				At age 7 yr
Sexuality; school and/or work plans	Counseling			Begin about age 10 yr	
Renal and liver dysfunction	Cr, BUN, LFTs, CBC	X		Begin about age 15 yr	
Metabolic dysfunction	Fasting BG and lipids			Begin about age 15 yr	
Low BMD	DEXA scan				At about age 18 yr
GH action	IGF-I/IGFBP-3			During GH tx	

BG, Blood glucose; BUN, blood urea nitrogen; CBC, complete blood count; cr, creatinine; Dx, diagnosis; DEXA, dual-energy x-ray absorptiometry; echo, echocardiogram; EKG, electrocardiogram; IGFBP-3, IGF binding protein-3; LFT, liver function test; SNHL, sensorineural hearing loss; TTG IgA Ab, tissue transglutaminase IgA antibodies; Q, every; tx, treatment.

[a] These guidelines were adapted from Davenport and Calikoglu (40) and Bondy (a guideline of the Turner Syndrome Study Group) (10) and reflect the author's clinical practice. They suggest minimal routine screening evaluations. If the patient has a problem in one or more areas, she will generally be followed up by a specialist in those areas and evaluated more frequently.

[b] If diagnosed in infancy or early childhood, an echocardiogram may be performed. An MRI should be obtained once the child is able to undergo an MRI evaluation without sedation.

of a pubertal growth spurt. The average girl with TS falls below the fifth percentile in length by 1.5 yr of age (2). Early growth failure is often exacerbated by poor suck, slow feeding, and frequent vomiting.

GH therapy is now standard of care for girls with TS (10). Studies have repeatedly demonstrated that GH accelerates growth and improves final adult stature, including a randomized, controlled trial in which girls treated with GH for a mean of 5.7 yr averaged 7.2 cm taller than those in the control group (11).

Most studies have demonstrated that adult height is maximized if GH therapy is begun at a young age and estrogen therapy is delayed (12). In a randomized, controlled 2-yr study of GH therapy initiated between 9 months and 4 yr (mean age 2.0 ± 1.0 yr), the mean height SD score (SDS) of girls with TS who received GH increased 1.1 SDS and was very close to average for the general population (−0.3 SD) (13). In contrast, height in the control group declined by 0.5 SDS, resulting in a 1.6 SDS (6.8 cm) between-group difference in height gain. Potential

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benefits of early GH therapy include decreased GH costs, rapid normalization of height, elimination of stature-related physical limitations, improved likelihood of being treated age-appropriately, and increased likelihood of pubertal induction at a normal age. It is now recommended that GH therapy be considered as soon as growth failure (decreasing height percentiles on the normal growth curve) is demonstrated (10). Typical doses of GH are 0.375–0.400 mg/kg · wk divided daily and given before bedtime. If monitoring (generally every 3–4 months) reveals poor growth, then noncompliance or a new TS-associated problem should be considered. GH is generally continued until the patient reaches a satisfactory adult height or it is no longer beneficial (growth rate <2 cm/yr).

Families should be fully apprised of the risks associated with GH therapy. A study of 5220 girls with TS who received GH revealed higher incidences, as expected, for scoliosis (0.39%), diabetes (0.19%), and serious cardiovascular events (0.32%) than for non-TS patients. However, incidences were also increased for intracranial hypertension (0.23%), slipped capital femoral epiphysis (0.24%), pancreatitis (0.06%), and new malignancies (0.11%). No adverse effects of GH on cardiac size, aortic diameter, or cardiovascular function have been found. Insulin resistance is increased during GH therapy but may actually be improved after discontinuation due to the beneficial effects of GH therapy on body composition (14).

A nonaromatizable anabolic steroid, such as oxandrolone at a dose of less than 0.05 mg/kg · d, may be given in conjunction with GH to accelerate growth further, usually in girls who are older than 8–9 yr of age and have extreme short stature (15, 15).

Young adults with TS who have received GH therapy and estrogen replacement therapy generally report a normal quality of life (QOL). In one study, height SDS gain had a significant positive effect on the outcome of role limitations due to physical health problems and daily activities (16), whereas height SDS was not correlated with QOL in another (17). Unfortunately, no QOL studies have been reported for randomized, controlled GH trials.

Cardiovascular disease and risk of aortic dissection

Congenital heart disease occurs in about 75% of fetuses and 25–45% of live-born girls with TS. The most common abnormalities are bicuspid aortic valve (16%) and coarctation of the aorta (11%); however, structural defects such as PAPVR and atrial and ventricular septal defects are also seen (18). At diagnosis, each patient should have an imaging study, generally echocardiography for young children and MRI for adolescents and adults. Girls that were imaged *in utero* should be reimaged. Children who had echocardiograms performed should be reimaged using MRI when they can do so without sedation. Frequent abnormalities that are detected by MRI but not visualized by echocardiogram include elongated transverse aortic arch, aberrant right subclavian artery, and PAPVR. Conduction or repolarization defects, including prolonged QT interval, have been described and attributed to neuroautonomic dysfunction. Therefore, an electrocardiogram should be performed along with the imaging studies.

Aortic dissection, an often fatal event, occurs in 1–2% of the TS population and is usually preceded by dilatation of the aortic root and/or ascending aorta. Dissection occurs relatively early in life at a median age of 35 yr (19). Longitudinal imaging every 5–10 yr to assess aortic diameters is recommended, even in those with a normal initial cardiac study. Patients should be encouraged to carry a medical alert card and demand evaluation for aortic dissection if they experience rapid onset of chest pain.

Epidemiological studies have revealed a 3-fold higher mortality in the TS population than the general population, with circulatory disease accounting for 41% of the excess mortality (11% from ischemic heart disease, 11% from cerebrovascular disease, 8% from aortic aneurysm, and 8% from congenital heart disease) (20). One of the major contributing risk factors for cardiovascular events is hypertension, which affects up to 25% of adolescents and 40–60% of adults with TS (18). Therefore, blood pressure (BP) should be measured at each clinic visit and ambulatory blood pressure monitoring used for more exacting diagnosis of hypertension and assessment of therapy.

Gonadal failure

Gonadal failure occurs in most individuals with TS. Germ cells in the genital ridges multiply normally into the millions by midgestation (21). Afterward, however, there is accelerated loss of oocytes in the 45,X ovary, leaving few follicles in a fibrous streak by birth. Approximately one third of girls with TS have spontaneous puberty, but only half of those complete puberty with menarche (22). Hypogonadal girls have an exaggerated biphasic pattern of gonadotropin secretion, with very high levels in infancy declining to a nadir at 7–8 yr of age and increasing by 9–11 yr to the menopausal range (23). Gonadotropin levels may be useful for predicting future gonadal function as well as determining appropriate timing and dosing of HRT (24).

The goals of estrogen replacement therapy in girls with TS are to normalize developmental changes in secondary sex characteristics including breast size and shape, uterine size and shape for possible reproductive function, bone growth and mineral accrual, cardiovascular function, brain development, liver function, and other estrogen-de-

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pendent processes. Early initiation of GH therapy (25, 26) and careful choice of estrogens, estrogen doses, and modes of delivery appear to allow initiation of estrogen therapy at a normal age but still allow a normal adult height to be attained. Low-dose systemic estradiol combined with GH may actually enhance final adult stature (27–29).

There are many options for HRT. However, systemic administration of estradiol, usually by transdermal application in a patch or gel, is the only form of therapy to achieve natural levels of estradiol in blood (30). If delivered orally, estradiol undergoes extensive hepatic first-pass metabolism, with most of it being transformed to estrone sulfate. Ethinyl estradiol, a potent synthetic estrogen with little hepatic metabolism, is not available commercially in the United States. Conjugated equine estrogen (CEE), the form of estrogen most widely used in the United States, contains multiple estrogens, progestins, and androgens, some of which are not found in humans. There is no justification for CEE use in children.

Estrogen deficiency could be the inciting or exacerbating factor in several problems associated with TS. Aromatase and estrogen receptors are widely expressed in reproductive and nonreproductive tissues. Estradiol deficiency causes cancellous bone loss, endothelial dysfunction, decreased insulin production, an abnormal lipid pattern, increased central adiposity, and early atherosclerosis. Indeed, oophorectomy is an independent predictor of myocardial infarction and coronary death. In estrogen-deficient individuals with TS, replacement therapy improves liver enzyme abnormalities and some cognitive deficits (short term memory, reaction time, and nonverbal processing speed) (31).

Although both oral and transdermal estrogens prevent atherosclerosis, oral estrogens increase resistance to activated protein C and decrease antithrombin III, increasing the risk of thrombosis (32). A case control study of 155 consecutive cases of women hospitalized with a first episode of idiopathic venous thromboembolism showed a 4-fold increased risk of pulmonary embolism for those taking oral estrogens *vs.* those taking transdermal estradiol (TDE) (33). Oral estrogens also increase C-reactive protein, an acute phase reactant that independently predicts cardiovascular disease; cause GH resistance, decreasing IGF-I and IGF binding protein-3 levels; increase SHBG, resulting in decreased testosterone availability; and cause triglyceride enrichment of low-density lipoprotein and high-density lipoprotein particles, making them more atherogenic. TDE has little effect on these parameters (34) .

None of these studies has been carried out in large randomized trials and most have involved postmenopausal women; therefore, their applicability to adolescents and young adults with TS remains to be proven. In a recent metabolic study of GH-treated girls with TS, neither oral nor transdermal estrogen adversely affected rates of protein turnover, lipolysis, or lipid oxidation rates. There were also no clinically significant changes in IGF-I, plasma lipids, or fibrinogen concentrations (35). In another study, prepubertal GH-treated girls with TS were randomized to oral conjugated estrogen or TDE for 1 yr. No differences were found in growth velocity, IGF-I, or lipid profile; however, the TDE group had significantly greater increases in spine bone mineral density (BMD) and uterine growth (36).

A suggested protocol for puberty induction using TDE patches is presented in Table 3. If TDE cannot be used, oral estradiol or ethinyl estradiol should be considered. The following doses are considered equivalent although equivalency depends on which assays and clinical end points are used: 100 μg TDE = 2 mg oral estradiol = 20 μg ethinyl estradiol = 1.25 mg CEE. Oral contraceptives should be avoided if possible because they have unnecessarily high estrogen/progestin concentrations.

Androgen replacement therapy is not standard of care; however, a recent randomized, double-blind, placebo-controlled, crossover pilot study of androgen replacement therapy (1.5 mg methyl testosterone) in TS demonstrated significant beneficial effects on bone health, lipid profile, body composition, and QOL, whereas cognitive functions were variably affected (37).

Developmental delays and learning disabilities

Although their overall level of intellectual functioning is within the average range, individuals with TS may have developmental delays in infancy and often have a pattern of cognitive, behavioral, and psychosocial functioning that is similar to nonverbal learning disabilities (NLD) (38). Individuals with TS tend to have difficulties in the following: 1) visuomotor skills such as writing and copying designs; 2) visual-spatial skills such as visual imagery, part-whole perception, mazes, and directional sense; 3) visual and working memory; 4) visual attention; 5) executive functions such as planning and problem solving; and 6) social skills and dealing with new situations (31, 38). Strengths include auditory processing skills as well as rote expressive and receptive language skills. Verbal IQ scores are generally higher than performance IQ. Differences in brain structure, including smaller parietal lobes, parietal-occipital, and prefrontal volumes correlate with differences in brain function (39). The concept of NLD is relatively new and may not be familiar to some educators. Nonetheless, with sufficient advocacy on the part of family, most girls with TS and NLD will receive accommodations in school.

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TABLE 3. Pubertal induction and maintenance estrogen therapy using TDE: a protocol using low growth-promoting doses for 18–24 months[a]

Treatment (months)	Target E2 (pg/ml)[b]	E2 dose	Notes
			Consider initiation of puberty at age 11–12 yr if there is no breast development.
0	3–4	0.1 μg/kg	Cut and apply a portion of a matrix patch to deliver 0.1 μg/kg E2. Apply in p.m. and remove in a.m.[c]
6	3–4	0.1 μg/kg	Wear a 0.1 μg/kg equivalent portion of the patch continuously. Change patch as directed (once or twice weekly). Check random E2 level to ensure E2 is in target range.
12	6–8	0.2 μg/kg	
18	~12	12.5 μg	E2 levels below this are believed to accelerate growth more than bone maturation.
24	~25	25 μg	
30	~37	37.5 μg	
36	~50	50 μg	Start progestin (earlier, if breakthrough bleeding occurs): 200–300 mg micronized oral progesterone for about 12 d/month qhs (causes drowsiness) or 5 mg oral medroxyprogesterone for about 12 d/month.
42	~75	75 μg	
48	50–150	100 μg	Typical adult dose; may not be high enough to protect liver, arteries, *etc.*

E2, 17β-Estradiol; qhs, before bedtime.

[a] This protocol is but one of many that can be used. This specific protocol is used in the author's clinic and individualized, depending on patient circumstances and desires. For example, older girls may want to be started at 25 μg.

[b] To convert picograms per milliliter to picomoles per liter, multiply by 3.671. E2 levels should be monitored using liquid chromatography/tandem mass spectroscopy technology.

[c] Vivelle Dot, matrix transdermal patch, is small and tends to adhere well. One-sixth to one-eighth of a 25 μg patch is approximately 0.1 μg/kg dose.

Approach to our patient

Our patient, like most girls who are diagnosed in the 10- to 15-yr-old range, was brought to attention for short stature but had numerous additional features of TS at diagnosis. Discussions about GH therapy were interesting, given that she was predicted to achieve a normal adult stature of about 155 cm (61 in.) without therapy (estimated by following her percentile on the TS growth chart to adulthood). The family chose to begin GH because K.S. considered herself short already, and they were concerned that loss of relative height over the next few years would place her at even greater social disadvantage. A decision was made to begin low-dose estrogen therapy 6 months later at 12 yr (Table 3).

The family was relieved to know that her social interactions, slow written output, and difficulties with math were common in TS and that some resources were available to help her. They were encouraged to join the TSS and given information about NLD and pertinent web sites (nlda.org, nldline.com and ldonline.org). They scheduled neurocognitive testing and planned to push for an individualized education plan for school. They were especially delighted to learn that many girls with TS and a NLD are allowed additional time for tests, including those that are standardized nationally.

Existing controversies

Very little of the care provided to individuals with TS is evidence based. Most recommendations are based on the advice of groups of clinician scientists with interests and expertise in the field. Consequently, there are innumerable areas of controversy. These include how to optimize screening evaluations (when to begin, what tests to use, and how often to repeat for associated morbidities), whether newborn screening for TS is desirable, whether fluorescent *in situ* hybridization or PCR for Y material should be routinely performed, whether all girls with TS diagnosed early should undergo developmental evaluations in infancy, which cardiac abnormalities constitute a contraindication for assisted pregnancy, and which options are best for hormone replacement therapy.

Areas of uncertainty

Many areas of uncertainty merit research and discussion, including the significance of cardiac MRI findings such as elongated aortic arch, the thresholds for BP that should be used to initiate or intensify antihypertensive therapy, the

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optimal timing and dosing of GH therapy, the risk of cancer that GH therapy confers in later life, the effect of GH on psychosocial attributes, whether keeping levels of IGF-I in the normal range mitigates that risk, methods to achieve adult quality care and enhance reproductive potential, and strategies for managing NLDs. Perhaps the largest area of uncertainty, however, is that of HRT. Discussions have largely concerned how to induce puberty and maintain normal sex steroid action during adulthood, yet many individuals with TS have a congenital deficiency of estrogen, evident in the elevated levels of gonadotropins in infancy. Perinatal steroids may imprint differentiated functions in later life. Therefore, research into the effect of estrogen deficiency in infancy and childhood are needed in addition to those for adolescents and adults. Estrogen and androgen action, including that in childhood, should be a focus of research in the care of the TS population. Until more data are available, it seems prudent to mimic normal estradiol physiology in adolescence and adulthood as closely as possible.

Acknowledgments

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