Clinical practice in Turner syndrome

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SUMMARY

Turner syndrome (TS) is a common genetic disorder, resulting from the partial or complete absence of one sex chromosome, and occurring in approximately 50 per 100,000 liveborn girls. TS is associated with reduced adult height and with gonadal dysgenesis, leading to insufficient circulating levels of female sex steroids and to infertility. Morbidity and mortality are increased in TS but average intellectual performance is within the normal range. A number of recent studies have allowed new insights to be gained with respect to epidemiology, genetics, cardiology, endocrinology and metabolism. Elucidation of the effects of short stature homeobox protein deficiency has explained some of the phenotypic characteristics in TS, principally short stature. Treatment with growth hormone during childhood and adolescence allows a considerable gain in adult height, although the consequences of this treatment in the very long term are not clear. Puberty must be induced in most cases, and female sex hormone replacement therapy (HRT) is given during adult years. The optimal dose of HRT has not been established and, likewise, the benefits and drawbacks of HRT have not been thoroughly evaluated. The risks of type 2 diabetes, type 1 diabetes, hypothyroidism, osteoporosis, congenital heart disease, hypertension, ischemic heart disease, aortic dilatation and dissection, inflammatory bowel disease and celiac disease are clearly elevated, and proper care during adulthood is important. Currently no firm guidelines for diagnosis exist. In conclusion, TS is a condition associated with a number of diseases and conditions that are reviewed in the present paper. Individuals with TS need life-long medical attention.

KEYWORDS cardiovascular diseases, estrogens, glucose metabolism, growth, growth hormone

REVIEW CRITERIA

For this review I concentrated on all papers published on Turner syndrome with special emphasis on the most recent literature. Papers relating to cardiology, especially aortic dissection, pediatrics, and the effects of estradiol in other conditions were also considered. The main source was PubMed, and the major endocrinology and cardiology journals.

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INTRODUCTION

Since the description of Turner syndrome (TS) by Henry H Turner in 1938, a wealth of information has come to light, and our current understanding of the syndrome has been broadened. The syndrome affects only females and it is clear that care must include the close collaboration of several specialties such as embryology, pediatrics, gynecology and obstetrics, endocrinology, cardiology, gastroenterology, otorhinology and ophthalmology.

In this review, I focus on the clinical aspects of TS, in particular the epidemiology, endocrinology, cardiology, gastroenterology, and gynecology, with reference to recent genetic discoveries.

DIAGNOSIS, EPIDEMIOLOGY AND GENETICS

The genetic background of the TS phenotype is highly variable, but includes complete or partial absence of one of the sex chromosomes (the X or Y chromosomes), with at least one X chromosome remaining.[1] The first described cases possessed the "classical" TS karyotype, 45X. It is now recognized that many patients with TS exhibit MOSAICISM, with the presence of two or more distinct cell lines. In newer series, the classical karyotype only accounts for 50% of cases; the remaining cases have karyotypes including mosaic karyotypes with the presence of both a 45X and a 46XX cell line, or with a whole or partial Y chromosome and karyotypes with an ISOCHROMOSOME of X (i[Xq] or i[Xp]).[2] The genetic basis of the TS phenotype is being unraveled with the description of the short stature homeobox (*SHOX*) gene, localized to the pseudoautosomal region on the X and Y chromosomes.[3,4] Haploinsufficiency of *SHOX* explains the reduction in final height, changes in bone morphology, sensorineural deafness, and other features associated with TS (see Box 1). Additional genes are thought to be involved in the pathogenesis of TS, and await description.

GLOSSARY

MOSAICISM
The presence in an individual of two or more unique cell lines, differing by genotype or chromosome complement

ISOCHROMOSOME
A chromosome resulting from fusion of identical chromosome arms, potentially leading to monosomy of one arm and trisomy of the other

Box 1 Short stature homeobox (*SHOX*) gene haploinsufficiency.

Haploinsufficiency of *SHOX* probably explains a large proportion of the recorded deficit in height (short stature), and probably also explains the short fourth metacarpal, cubitus valgus, Madelung deformity, mesomelic growth, high arched palate, micrognathia, sensorineural deafness and dysproportionality of skeletal size. Haploinsufficiency of *SHOX* probably does not explain the entire deficit in final height, and also probably not the congenital cardiovascular malformations and endocrine disturbances, estrogen deficiency and infertility, increased mortality and other stigmata known to appear in Turner syndrome. *SHOX* is expressed in the pancreas but it is unknown whether this explains the β-cell dysfunction seen in Turner syndrome.

The prenatal prevalence of TS is much higher than the postnatal prevalence,[2] and there is a well-described increased intrauterine mortality.[5] Prenatal diagnosis of TS is not always correct; therefore, a more precise diagnosis should include high-resolution ultrasound or fetal echocardiography, and other modern modalities. A European multicenter study found a termination rate of 66%, which suggests that most diagnosed fetuses with TS are legally aborted.[6] That study confirmed previous studies showing legal abortion rates of 60–80%;[2] however, only a fraction of girls with TS (less than 10%) will be diagnosed prenatally.[2]

Figures for the prevalence of TS are based on a number of cytogenetic studies with estimates ranging from 25–210 per 100,000 females,[7] and a hypothetical proportion of about 50 per 100,000 girls in white populations might be agreed upon (Figure 1).

Most postnatal diagnoses are made at birth (15%), during teenage years (26%), and during adulthood (38%), with the remainder being diagnosed during childhood;[8] this represents a substantial delay in diagnosis for the majority of patients (Figure 2). Interestingly, the most common trigger for diagnosis during infancy is lymphedema (97% of cases), and during childhood and adolescence is short stature (82% of cases).

Morbidity is clearly increased in TS. In a study of all women in Denmark that compared all diagnosed females with TS with the background population of women, we calculated incidence rates for diseases that are suspected to occur with increased frequency in TS.[9] The relative risk (RR) of an endocrine diagnosis in TS patients is significantly increased to 4.9 (95% CI 3.6–6.4), which is accounted for by a significantly increased risk of hypothyroidism (RR 5.8; CI 1.2–16.9), type 1 diabetes mellitus (RR 11.6; CI 5.3–22.0), and type 2 diabetes mellitus (T2DM, RR 4.4; CI 2.4–7.7). The risks of ischemic heart disease and arteriosclerosis (RR 2.1; CI 1.2–3.3), hypertension (RR 2.9; CI 1.2–6.0), and vascular disease of the brain (RR 2.7; CI 1.04–5.30), were significantly increased. The risk of other conditions such as cirrhosis of the liver (RR 5.7; CI 1.6–14.6), osteoporosis (RR 10.1; CI 2.2–30.9), and fractures (RR 2.16; CI 1.50–3.00) was also significantly increased, as were the risks for congenital malformations of the heart, of the urinary system, and of the face, ears, and neck. The RR for all cancers was 1.35 (CI 0.70–2.35), however, with only the risk of colonic and rectal cancers being significantly elevated (RR 4.94; CI 1.02–14.45).[9,10] Congenital malformations are most frequent among women with the 45X karyotype, whereas endocrine diseases, acquired heart disease, hypertension, and arteriosclerosis are more frequent in women with other TS karyotypes.[9]

Mortality is also increased in TS. In a British cohort study, the RR of premature death was increased to 4.2 (CI 3.2–5.4),[11] with increases due to diseases in the nervous, digestive, cardiovascular, respiratory and genitourinary systems. The number of deaths due to cancer was comparable to that in other women, corroborating morbidity studies. Earlier, Price *et al.*[12] also found overall mortality to be increased threefold, especially in females with congenital malformations. Furthermore, aortic dissection was a frequent cause of death. Omitting patients with congenital malformations from the statistical analysis reduced the mortality ratios to normal levels.

TS is characterized clinically and no firm guidelines for diagnosis exist;[13] however, the cardinal features include growth retardation with reduced adult height (with or without additional phenotypic features) and, except in rare cases, gonadal insufficiency and infertility. Congenital malformations and conditions that are often seen in TS are given in Table 1 with tentative frequencies.

OVARIAN INSUFFICIENCY

Early ovarian demise is seen in most patients with TS, and estrogen insufficiency ensues. The germ-cell count of a fetus with TS is normal until week 18 of gestation, after which accelerated degeneration takes place.[14] High levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are present in early childhood (2–5 years) and after the time of normal onset of puberty (11 years).[15] In adulthood the levels of FSH and LH are increased to menopausal levels. Many untreated girls show signs of puberty or have regular periods for varying lengths of time.[16] This might be explained by new data showing that follicles can still be found in girls 12–19 years of age, even in some 45X patients.[17] Understanding the processes involved in early follicular apoptosis (programmed cell death) in TS might in the future lead to development of a treatment that can spare the follicles and maintain fertility. Despite recent advances it is still not clear why accelerated apoptosis takes place in early TS, and it might indeed occur via more than one pathway. 'Death by defect' and apoptosis due to faulty meiotic pairing are theories that could possibly be explanatory,[18] but low levels of growth factors (including insulin-like growth factor 1 and insulin) or high levels of LH could also contribute.[19]

The ideal timing of endocrine therapy allows induction of puberty in conjunction with the patient's peers to avoid social problems at school because of delayed physical and psychologic development. This would also allow optimal bone mineralization to take place (see below). In most normal girls puberty starts around 12 years of age. Since 30% of girls with TS undergo some spontaneous pubertal development and 2–5% have spontaneous menses and might achieve pregnancy without medical intervention,[16,20] signs of puberty should be looked for before starting estrogen therapy. When FSH and LH are clearly elevated and clinical signs of puberty are absent, pubertal induction should be started. It can be postponed for a while, if the individual patient does not suffer from psychologic distress because of lack of signs of puberty when comparing herself to peers. If spontaneous pubertal development occurs, it is in most cases followed by progressive premature ovarian failure.

In order to induce pubertal development, the dosing and timing of estrogen therapy should aim at mimicking normal pubertal development. Doses should be individualized, starting with very low doses of estrogen as monotherapy, which can be monitored in terms of the development of secondary sex characteristics, serum LH and FSH, bone maturation or uterine volume. A gestagen (artificial progesterone)

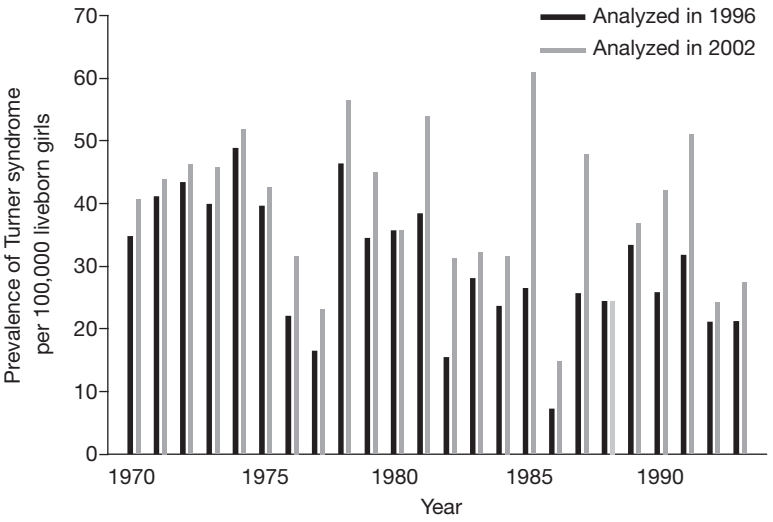

Figure 1 Prevalence of Turner syndrome by year of birth (1970–1993) in Denmark. Black bars illustrate the prevalence when studied in 1996; gray bars illustrate the prevalence when studied in 2002, indicating the consistent rise in the diagnosis of Turner syndrome, even after the age of 20 years. The data underline the fact that Turner syndrome is often diagnosed late, and do not indicate a true increase in prevalence. Data are from the Danish Central Cytogenetic Register.

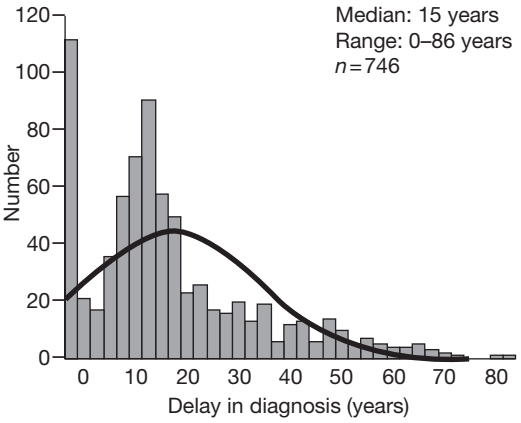

Figure 2 Delay in Turner syndrome diagnosis from birth. The X-axis indicates the chronologic age at diagnosis of Turner syndrome, with each bar illustrating a 2.5-year period. Data are from the Danish Cytogenetic Central Register from 1910–2000 and include all females with a karyotype that can be associated with Turner syndrome.

Table 1 Abnormalities associated with Turner syndrome and their tentative frequencies.[9,42,45,60,65,77–79]

Category	Feature	Frequency (%)
Height	Retarded growth and reduced adult height	95–100
Gonadal	No pubertal development	85
	Infertility	98
	Chronic estrogen deficiency	95–98
	Androgen insufficiency	?
Endocrine	Glucose intolerance	15–50
	Type 2 diabetes mellitus	10
	Type 1 diabetes mellitus	?
	Thyroiditis and hypothyreosis	15
	Hypertension	50
	Android body composition	?
Gastrointestinal and hepatic	Elevated hepatic enzymes	50–80
	Celiac disease	8
	Inflammatory bowel disease	2–3
Eyes	Epicanthus	20
	Nearsightedness	20
	Strabismus	15
	Ptosis	10
Ears	Infection of middle ear	60
	Hearing defects	30
	Deformity of external ear	15
Mouth	Micrognathia (small mandibular bone)	60
	High arched palate	35
	Abnormal dental development	?
Neck	Low posterior hairline	40
	Broad short-appearing neck	40
	Pterygium colli (webbed neck)	25
	Excess loose skin in the back of the neck of newborns	25
Thorax	Broad chest (shield chest) with widely spaced nipples	30
	Inverted nipples	5
Skin, nails, and hair	Increased skin ridge count	30
	Lymphedema of hands and feet at birth (or later)	25
	Multiple pigmented nevi	25
	Nail hypoplasia	10
	Vitiligo	5
	Alopecia	5
Skeletal	Bone age retardation	85
	Decreased bone mineral content	50–80
	Cubitus valgus	50
	Short fourth metacarpal	35
	Genu valgum	35
	Congenital hip luxation	20
	Scoliosis	10
	Madelung deformity	5
Cardiac	Bicuspid aortic valves	14–34
	Coarctation of the aorta	7–14
	Aortic dilation/aneurysm	3–42
Renal	Horseshoe kidney	10
	Abnormal positioning or duplication of renal pelvis, ureters or vessels	15
	Renal aplasia	3
Psychosocial[a]	Emotional immaturity	~40
	Specific learning problems	~40
	Mental problems	~25
	Neurocognitive deficits	?
Other	Poor thriving during first year of life	50

[a]The data are inconsistent, and these percentages should be viewed with caution.

is added when breakthrough bleeding occurs. Estrogen therapy should be coordinated with the use of growth hormone (GH); these treatments should be individualized for each patient, so as to optimize both growth and pubertal development. When growth is a priority, delaying estrogen therapy is an option, to avoid compromising adult height;[21] however, recent growth-promoting trials have documented that a physiologic timing of estrogen therapy does not compromise adult height, when GH therapy is started early and dose is increased stepwise (see below).[22,23]

Proper estrogen replacement during puberty has positive effects on motor speed, and on verbal and nonverbal memory and processing.[24] Females with Turner syndrome present with a particular neurocognitive profile, with impaired performance on motor tasks and impaired visual-spatial ability, but normal verbal skills.[25] The deficits in cognition are probably caused by haploinsufficiency of X-linked genes that normally escape X-inactivation, and these putative genes await further description.[26]

Infertility is rated by women with TS as the most prominent problem associated with the syndrome.[27] Oocyte donation is an option in many countries. The most recent studies show good results comparable to oocyte donation in other groups of patients.[28] Prolonged treatment with high daily doses of estradiol (4–6 mg or up to 8 mg of 17β-estradiol) might better prepare the uterus for implantation by increasing uterine size and endometrial thickness.[28]

Women with TS exhibit androgen insufficiency due to lack of the ovarian component of hormone production (especially testosterone), although the androgen contribution from the adrenals is intact.[29] So far substitution therapy with androgens has not been evaluated in women with TS.

DECREASED STATURE IN TURNER SYNDROME

Final height is decreased in TS, and this fact forms the basis for growth-promoting therapy in TS. Growth is already decreased *in utero*, and is slow during childhood.[30] The normal pubertal growth spurt is absent, even in girls with spontaneous puberty.[31]

Children with TS are given GH as a strategy to increase their final height regardless of whether there is a lack of GH or insulin-like growth factor 1, its effector hormone. Several studies suggest that GH production is reduced,[32,33] whereas others have found a normal GH secretion.[34]

Two studies have shown that final height can be almost normalized when an escalating dosing regime is used, and if GH treatment is started at an early age (4–6 years).[22,35] Results of the recent Canadian randomized controlled trial also demonstrated that final height could be enhanced by a mean of 7.2 cm, using a rather conservative dosing regime. Since it is the first randomized trial (and probably the only one ever to be conducted), it adds very important validity to the use of GH in this disease entity. These recent studies have emphasized four aspects of the findings from previous studies: an early start of GH treatment is important; escalating dosing regimes can overcome the waning effect of GH treatment observed after 1–2 years of administration; starting pubertal induction with estrogen at an age appropriate in comparison with the peers of the girls who have TS does not compromise growth; and a normal adult height can be attained in TS.

Treatment with GH seems to be safe in TS, but since large doses have recently been introduced, continued monitoring is also needed after termination of GH treatment in order to detect any late untoward effects of the treatment. GH induces INSULIN RESISTANCE, which subsides after treatment,[36] but since T2DM is already very frequent in patients with TS, there have been fears that an increase in T2DM could be seen due to treatment. GH treatment does not seem to affect blood pressure or left-ventricle morphology,[37] but increases the risk of otitis media and joint disorders.[23,38]

Body composition is highly distinctive in TS,[39] and might be considered disproportionate. It has been feared that GH treatment might lead to further changes in morphology, causing a disproportionate increase in the size of the feet and hands of adolescents with TS,[40] and more research will be needed in this area.

TURNER SYNDROME AND THE HEART

Much of the increased morbidity and mortality noted in TS is attributable to a range of heart conditions. Some of these are congenital and others are acquired.

TS is associated with congenital malformations such as coarctation of the aorta, other congenital malformations of the heart, and with horseshoe kidney and pterygium colli[41,42] (Figure 3).[43]

GLOSSARY

INSULIN RESISTANCE
A metabolic state characterized by an impairment in the ability to clear glucose at a given plasma insulin concentration

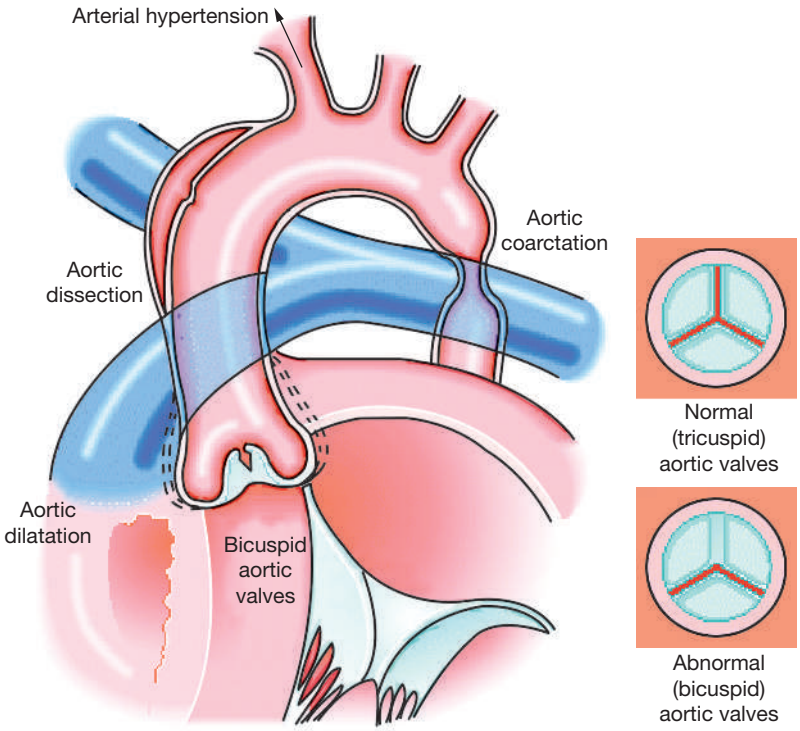

Figure 3 Illustration showing the typical congenital cardiovascular malformations seen in Turner syndrome—coarctation of the aorta, and bicuspid aortic valves, as well as the occurrence of aortic dilatation and dissection. Please note that presence of congenital malformations and/or systemic hypertension is not a prerequisite for the development of dilatation and dissection of the aorta.

GLOSSARY

MARFAN SYNDROME
Connective tissue disorder caused by fibrillin-1 gene mutation; risks include dilatation of the aortic root, and subsequent aortic dissection

The prevalence and the nature of cardiovascular malformations have been described in several studies (Table 1), and, overall, these malformations are present in at least 25% of patients with TS. The malformations predominantly involve the vessels of the left side of the heart, although right-sided malformations have also been documented; a recent study using MRI described partial anomalous pulmonary venous return (13%) and persistent left superior vena cava (13%), in addition to the well-known left-sided malformations.[44] Malformations were present in 50% of the women. The cause of congenital heart defects in TS remains unknown.

A bicuspid aortic valve is the most common cardiovascular finding in TS, and is seen in 13–34% of patients, compared with only 1–2% of the general population. Coarctation of the aorta is present in 4–14% of all patients with TS. Most patients with aortic coarctation are diagnosed early, because of the relative severity of the condition. Other malformations affecting the valves have also been reported (Table 2).

An increased aortic-root diameter, which is a risk factor for developing aortic dilatation and later rupture, is often seen and probably depends primarily on blood pressure,[45] although other factors might also contribute. Prospective studies are needed in order to determine how the risk of aortic dissection can be reduced. Currently, the approach is to reduce blood pressure and monitor the aortic-root diameter.

More than 60 case reports of aortic dilatation or dissection, some of which were fatal, have been described.[43] In most cases, associated risk factors were present. In the general population, risk factors for aortic dissection include systemic hypertension, congenital bicuspid aortic valves, and coarctation of the aorta.[46] In the reported cases of aortic dissection in TS, the abovementioned risk factors are usually, but not always, known to be present.[47] Currently, no biochemical or specific genetic abnormalities of the aortic wall have been identified in TS, but cystic medial necrosis, as found in MARFAN SYNDROME, has been described in some cases.

In addition to an increased frequency of aortic dilatation, the large arteries are also affected in TS. Baguet *et al.* found an increase in carotid intimal thickness, aortic augmentation index and pulse-wave velocity, findings that point towards both morphologic and functional abnormalities in the large arteries.[48] Aortic stiffness has also been found previously; this condition responds to treatment with female hormone replacement therapy (HRT).[49]

Pregnancy is a rare event in TS;[50] however, owing to an increasing number of egg donation programs, more patients can be expected to go through pregnancy in the future. Because of the pregnancy-associated changes in blood pressure and cardiac workload the risk of aortic dissection is likely to be increased. Successful, uneventful pregnancies have been reported; however, fatal and nonfatal maternal aortic dissections have also been described.[51]

Hypertension occurs early and with increased frequency in TS. Overall, 30% of children with TS are mildly hypertensive, 50% have an abnormal diurnal blood pressure profile,[52] and up to 50% of adult patients have clinical hypertension with an abnormal diurnal blood pressure profile.[45,53] Treatment with HRT has been shown to induce a significant reduction in diastolic blood pressure.[53] The heart rate is uniformly increased in TS; this is only partly explained by a decreased exercise capacity.

Table 2 Number and percentage of patients with congenital malformations in Turner syndrome, compiled from five studies with apparently unbiased inclusion of patients.

Malformation	Dawson-Falk *et al.*[41] (*n* = 40)[a]	Gotzsche *et al.*[42] (*n* = 179)[b]	Sybert[43] (*n* = 244)[b]	Mazzanti and Cacciari[80] (*n* = 594)[c]	Ho *et al.*[44] (*n* = 85)[d]
Coarctation of the aorta	5 (12.5%)	18 (10%)	34 (14%)	41 (6.9%)	10 (12%)
Dilated ascending aorta	5 (12.5%)	–	–	17 (2.9%)	–
Hypoplastic aortic arch	1 (2.5%)	–	–	–	–
Bicuspid aortic valve	7 (17.5%)	25 (14%)	33 (14%)	74 (12.5%)	–
Mitral-valve prolapse or regurgitation	2 (5%)	1 (0.6%)	6 (2%)	53 (8.9%)	–
Interrupted inferior vena cava with continuation of azygos vein	1 (2.5%)	–	–	–	–
Cardiac dextroposition	1 (2.5%)	1 (0.6%)	–	–	–
Aortic valve disease (stenosis and/or incompetence)	–	19 (11%)	14 (6%)	19 (3.2%)	–
Partial anomalous pulmonary venous drainage	–	1 (0.6%)	1 (0.5%)	17 (2.9%)	11 (13%)
Persistent left superior vena cava	2 (5%)	–	–	–	11 (13%)
Ventricular septal defect	–	–	–	3 (0.5%)	–
Atrioventricular septal defect	–	–	12 (5%)	1 (0.2%)	–
Pulmonary valve abnormality (stenosis, regurgitation)	–	2 (1%)	–	–	–
Persistent ductus arteriosus	–	2 (1%)	1 (0.5%)	–	–

[a]Patients examined by MRI scan and echocardiography. [b]Patients only given clinical examination and echocardiography. [c]Patients given clinical examination, electrocardiogram, chest X-ray, and transthoracic echocardiography. [d]Patients examined by MRI scan only. "–", not reported.

Epidemiologic data point towards an increased frequency of ischemic heart disease (acute myocardial infarction and arteriosclerosis).[9] Abnormalities in lipid profiles have not been reported in most studies with an appropriate control population,[54] although one study reported a slightly atherogenic lipid profile.[55] Proinflammatory markers of atherosclerosis (e.g. C-reactive protein and interleukin-6) are increased in TS.[56]

No long-term studies have assessed the impact of HRT on the heart and its potential role in the increased mortality seen in TS. It might be speculated that HRT would have positive effects on aortic stiffness in the long term,[49] but any direct effect on the aortic wall has not been described. Many patients do not receive HRT during adulthood, and many adolescents are introduced to estrogens rather late, in order to achieve an increased adult height. Likewise, the question of when to stop HRT, if ever, is unresolved. Three major studies in postmenopausal women have shown that HRT should not be used in this population as primary or secondary intervention against cardiovascular disease,[57,58] or as secondary intervention against strokes;[59] however, the applicability of these studies to a population of women with TS is dubious, given the fundamental differences between postmenopausal women and women of the normal child-bearing age with TS.

A number of issues remain unresolved: the cardiovascular pathophysiology, especially during adulthood, is not described in any great detail; there are few long-term follow-up studies; it is not known how aggressively hypertension should be treated, and which drugs should be chosen as first-line therapy. The concept of aortic dilatation in particular needs to be dealt with in greater detail—for example, the impact on the aorta of antihypertensive treatment and the long-term use of HRT. Similarly, it is not known how dangerous child-bearing might be for women with TS.

A cardiovascular risk profile should be determined at diagnosis, during adolescence, and in adulthood, and the patient informed about the risks and benefits of GH and HRT. Patients should be seen by a cardiologist, and undergo echocardiography together with clinical

Box 2 Clinical practice for patients with Turner syndrome, with respect to the heart and the great vessels.

- Echocardiography should be performed in all patients at diagnosis. If this is normal, or near-normal, repeat echocardiography should then be performed in adolescence, in adulthood, and probably every 5 years thereafter. A close working relationship with a cardiologist with knowledge of Turner syndrome is of great value.
- If congenital cardiac malformations are diagnosed, these should be dealt with appropriately (see text). This includes surgery, if deemed clinically necessary, regular clinical examinations (echocardiography, MRI scan, blood tests, blood pressure, etc.) and prophylaxis for infectious endocarditis (visits to the dentist, minor surgery, etc.).
- The potential consequences of growth-hormone treatment should be evaluated.
- The benefits and drawbacks of hormone replacement therapy should be discussed with the patient at a relevant age. At present hormone replacement therapy is recommended.
- There should be evaluation of the aorta, with emphasis on aortic dilatation and the subsequent risk of aortic dissection.
- Cardiac monitoring should take place prior to assisted reproductive therapy or unassisted pregnancy, and during pregnancy.
- The risk of ischemic heart disease should be discussed.
- Blood pressure should be monitored at every visit to the physician.

examination (Box 2). It might be prudent to perform a new cardiovascular assessment when pubertal induction is taking place, as well as in adulthood.[13] The potential effects of GH on the heart and great vessels should be discussed, as well as the consequences of HRT, and perhaps especially the consequences of not taking HRT. On the basis of the available literature, HRT is recommended during adulthood. The unsolved problem of knowing which patients will eventually develop dilatation of the aorta, and thus be at great risk of later aortic dissection, leaves the patient and her physician in a situation where, at present, the only solution is periodic echocardiography. Currently, it is not known how frequently echocardiography (and/or MRI) should be performed. It is recommended to take precautionary steps before and during pregnancy, whether the pregnancy is medically assisted or not, with cardiac monitoring (heart auscultation, blood-pressure measurement, and echocardiography) being performed at regular intervals. MRI should only be performed as part of cardiac monitoring during pregnancy on vital indication.

GASTROENTEROLOGY AND HEPATOLOGY

Increased levels of liver enzymes, especially alkaline phosphatase, alanine–aspartase aminotransferase and γ-glutamyl transferase (markers of hepatic injury or cell turnover) are very frequent in TS,[60] whereas bilirubin excretion and coagulation parameters are within the normal range in most cases

In a recent study of liver biopsies in 27 women with TS, taken because of persistently elevated liver tests,[61] multiple abnormalities were found; these included marked nodular regenerative hyperplasia ($n=6$), multiple focal nodular hyperplasia ($n=2$), and cirrhosis ($n=2$), in some cases associated with obliterative portal venopathy. Other patients showed moderate changes, including portal fibrosis, inflammatory infiltrates, and non-alcoholic fatty liver disease. The authors conclude that the main causes of liver abnormalities in TS are vascular disorders, thought to be congenital in origin, and non-alcoholic fatty liver disease. Signs of liver toxicity resulting from concomitant estrogen therapy were absent. The study is important for several reasons: it is the largest; it includes liver biopsies as well as thorough evaluation of other causes of liver disease; it excludes viral, autoimmune and alcoholic causes; and it excludes estrogen therapy as an etiologic agent in the liver abnormalities. Studies have actually shown that treatment with HRT tends to normalize measures of liver function.[62,63]

Inflammatory bowel disease (IBD) also seems to occur more frequently in TS (2–3%),[64] and should be particularly suspected in girls that do not respond to GH therapy. Celiac disease is present in 8% of patients, according to an Italian study,[65] and is also a potential cause of growth stunting. The usual guidelines should be followed for IBD and celiac disease.

GLUCOSE METABOLISM AND TYPE 2 DIABETES

Many girls and women with TS exhibit impaired glucose intolerance (present in about 50% of adult women) during an oral glucose tolerance test, and many develop T2DM.[9,53] Most patients with TS have normal fasting glucose and insulin levels before developing T2DM, and the data point towards a primary β-cell failure during glucose loading,[53,66] rather than insulin resistance as the initial defect that eventually leads to overt diabetes. This propensity to develop T2DM is related to low maximal oxygen uptake,

as shown during ergometer testing, and many women with TS have a low level of physical activity.[53,54] Whether low activity is an intrinsic part of the syndrome, or rather a consequence of 'being different', is presently unclear.

We have also found an increased frequency of type 1 diabetes in a register-based epidemiologic study,[9] a finding that has so far not been confirmed by others; however, clinical experience supports our finding.

Treatment of diabetes in TS is no different than in other diabetic conditions, and since many women with TS are obese, drugs such as metformin and thiazolidinediones are preferred as initial treatment, although many patients will progress to using insulin.

DISEASES OF THE BONE

Peak bone mass depends on a number of factors, such as genetic background, nutrition, physical activity, local growth factors, and a number of hormones. In TS, estradiol secretion is clearly deficient during childhood and adolescence.[67] Children, and younger and middle-aged adult patients, with TS have low BMD.[68,69] Studies show that fracture risk is increased (Figure 4),[9,70,71] pointing towards a clinical consequence of the decreased BMD. HRT is considered crucial to avoid a rapid decrease in BMD, and to induce maximal peak bone mass in adolescents and young adults.[68] This is supported by longitudinal studies of estrogen-deficient and estrogen-replete adolescents with TS. Patients with spontaneous menstruation had normal BMD, whereas patients without menstruation had reduced BMD.[72]

A 3-year longitudinal study of 21 women with TS (aged 20–40 years) that compared iliac crest biopsies taken before and 3 years after treatment with HRT showed compelling effects of estrogen on bone. Treatment consisted of estradiol implants and cyclic oral gestagen,[73] resulting in estradiol levels comparable to levels in premenopausal women, and considerably higher than levels achieved with regimens used hitherto (2 mg oral estradiol or equivalent transdermal doses). Bone biopsies pointed towards an anabolic effect of estradiol on the skeleton in young women with TS.[73] Further, GH might improve BMD. In a recent 7-year study with GH treatment given at three different doses, BMD increased in a dose-dependent manner.[74] However, estrogen was added after 4 years of GH treatment, and it is difficult to differentiate between the individual effects of GH and estrogen in this study.

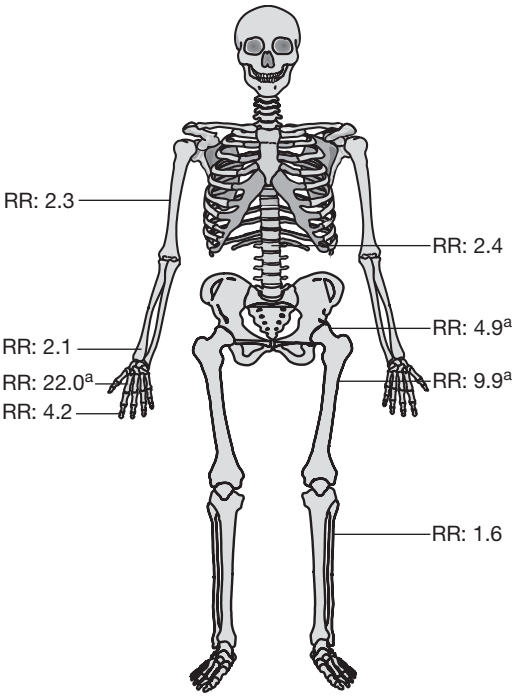

Figure 4 Site-specific risk of fractures expressed as relative risk (RR).[5] The overall RR for fractures is 2.18[a]. [a]Statistical significance ($P<0.05$). Adapted from Gravholt *et al*.[9]

No studies (either follow-up or intervention studies) of the effect of estradiol over the very long term have been published. There is a definite need for such studies to determine the ideal treatment regimen during adolescence in order to achieve two goals: attaining maximal peak bone mass and maintaining BMD without compromising adult height; and, with appropriate timing of pubertal induction, to achieve appropriate secondary sex characteristics. Furthermore, the dosage of estrogen during adult life has to be determined.

THYROID DISORDERS

Thyroid dysfunction is common in TS.[75] Hypothyroidism is frequent, eventually developing in as many as 30% of TS patients, and thyroid antibody formation is even more frequent. A recent study showed a considerable increase in new cases of hypothyroidism during a 5-year follow-up period.[76] The treatment of hypothyroidism follows normal guidelines.

It remains an enigma why so many TS patients suffer from diseases related to autoimmunity, and the cause of this grossly increased risk of

Box 3 Suggested clinical outpatient program for patients with Turner syndrome.

Baseline
Karyotype
Renal and pelvic ultrasound
Echocardiography
Thyroid status and antibodies
Celiac screen
Gonadotropins
Renal and liver function
Bone densitometry (dual energy X-ray absorptiometry scan)

Annual
Physical examination, including blood pressure and heart auscultation
Thyroid function
Body composition status (BMI <25 kg/m^2), including physical exercise and diet instruction
Fasting lipids
Fasting blood glucose
Renal and liver function

Every 3–5 years
Echocardiography
Bone densitometry (dual energy X-ray absorptiometry scan)
Audiogram
Celiac screen
Thyroid antibodies (thyroid peroxidase)

autoimmune diseases, including celiac disease, and diabetes (see above) is unknown; a genetic basis seems probable, although it is not documented. GH treatment does not increase the frequency of autoantibody production.

CONCLUSIONS

In summary, care of the patient with TS involves assessment of glucose metabolism, weight, thyroid function, bone metabolism, blood pressure, liver function, and cardiovascular status (Box 3). Estrogen deficiency should be treated, preferably with natural estrogens and a gestagen.

Knowledge concerning TS is still very limited—the syndrome is only seen infrequently by most clinicians, and patients typically have a range of questions related to the syndrome at first consultation. Patients with TS need comprehensive care, preferably from a centralized, multidisciplinary team that incorporates cardiology, gynecology (including a fertility clinic), otorhinology, ophthalmology and gastroenterology. This care can best be provided by an outpatient clinic with special emphasis on TS.

KEY POINTS

- Turner syndrome is often diagnosed late with a median delay of 15 years
- Short stature can be treated with growth hormone and a considerable increase in final height can be achieved
- Ovarian insufficiency from adolescence is present in most patients and should be treated with hormone replacement therapy
- Early detection of a number of diseases is possible, but requires continued surveillance
- Heart conditions are often seen and should be screened for
- A specialized, multidisciplinary team should take care of adolescents and adults with Turner syndrome in order to improve early detection and treatment of associated disorders

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