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Standardized Multidisciplinary Evaluation Yields Significant Previously Undiagnosed Morbidity in Adult Women with Turner Syndrome

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Context: Besides short stature and gonadal dysgenesis, Turner syndrome (TS) is associated with various abnormalities. Adults with TS have a reduced life expectancy, mainly related to structural abnormalities of the heart and aorta, and an increased risk of atherosclerosis.

Objective: Our objective was to investigate the yield of an initial standardized multidisciplinary screening in adult TS patients.

Design and Setting: This was an observational study at a multidisciplinary care unit for adult women with TS.

Participants: Participants were adult women with TS ($n = 150$). Mean age was 31.0 ± 10.4 yr, with 47% karyotype 45,X.

Interventions: All women were consulted by an endocrinologist, a gynecologist, a cardiologist, an otorhinolaryngologist, and when indicated, a psychologist. The screening included magnetic resonance imaging of the heart and aorta, echocardiography, electrocardiogram, dual-energy x-ray absorptiometry, renal ultrasound, audiogram, and laboratory investigations according to international expert recommendations.

Main outcome measures: New diagnoses and prevalence of TS-associated morbidity were evaluated.

Results: Thirty percent of patients currently lacked medical follow-up, and 15% lacked estrogen replacement therapy in the recent last years. The following disorders were newly diagnosed: bicuspid aortic valve ($n = 13$), coarctation of the aorta ($n = 9$), elongation of the transverse aortic arch ($n = 27$), dilation of the aorta ($n = 34$), osteoporosis ($n = 8$), osteopenia ($n = 56$), renal abnormalities ($n = 7$), subclinical hypothyroidism ($n = 33$), celiac disease ($n = 3$), glucose intolerance ($n = 12$), dyslipidemia ($n = 52$), hypertension ($n = 39$), and hearing loss warranting a hearing aid ($n = 8$). Psychological consultation was needed in 23 cases.

Conclusions: Standardized multidisciplinary evaluation of adult women with TS as advocated by expert opinion is effective and identifies significant morbidity. Girls with TS benefit from a careful transition to ongoing adult medical care. (*J Clin Endocrinol Metab* 96: E1517–E1526, 2011)

Turner syndrome (TS) is the result of complete or partial absence of one X chromosome and one of the most common sex chromosomal abnormalities with an incidence of approximately one in 2000 in live-born girls (1). Besides short stature, gonadal dysgenesis, and dysmorphic features, TS is associated with a wide range of abnormalities affecting nearly every organ system. Girls with TS are usually treated with GH to increase adult height and with estrogens to induce puberty. Hormone replacement therapy (HRT) has to be started either after induction of puberty or when estrogen production becomes insufficient after initial spontaneous puberty.

Also in adulthood, TS is associated with significant morbidity. There is an approximately 3-fold increased age-related risk of mortality mainly caused by structural cardiovascular anomalies and atherosclerosis related to hypertension, diabetes, and dyslipidemia (2). In addition, women with TS are prone to develop hypothyroidism, osteoporosis, hearing loss, neurocognitive deficits, and emotional problems (3, 4). In recent years, the enhanced morbidity and mortality in adults with TS as well as the ensuing need for regular medical attention are increasingly recognized. Especially the transition from pediatric to adult care is a point of concern. Many young women are lost to regular medical follow-up after discharge from the pediatric clinic. Several specialized TS clinics have been established in the United States and Europe to provide a coordinated multidisciplinary care service. Based on the experience of these centers, recommendations for standard of care and periodic screening have been put forward (5–7). Despite these efforts, however, adult women with TS often lack appropriate medical attention (8–12). In a young French TS population, only 3.5% received appropriate medical care (8). In an adult U.S. TS population, only one third had undergone the three examinations considered standard care for TS women, *i.e.* cardiac and renal ultrasound and audiology (10). In a Belgian cohort, 12.7% lacked medical attention despite reported health problems and 14.5% lacked HRT (9). An inventory among Dutch TS women previously followed at a single pediatric clinic showed that appropriate specialist care was continued in only a minority (12).

Our multidisciplinary care unit for TS women was established in 2005 and is the largest facility in The Netherlands. Our approach was adapted from international guidelines for care in TS patients (5–7). The yield of screening as advocated in these guidelines was not previously examined. In light of the question of whether the burden of screening is justified by the yield of new diagnoses, and whether the approach is cost-effective, the aim of this study was to investigate the yield of an initial comprehen-

sive screening for TS-associated morbidity in a large group of adult patients in a single Dutch center.

Patients and Methods

Patients

The study included 150 consecutive adult TS patients who underwent an initial evaluation between May 2005 and June 2009. Mean age was 31.0 ± 10.4 yr. The diagnosis of TS was established by standard karyotyping of 30 peripheral lymphocytes (Table 1) (5).

Seventy-six percent of the women had received regular pediatric care during childhood, and 56% of the women had been treated with GH. Of 150 patients, 26 were directly referred for transition from pediatric to adult care within our center. Seventy-nine patients already received regular medical care by either a gynecologist, cardiologist, and/or endocrinologist. Forty-five patients had lacked medical follow-up by any specialist, with a mean period of approximately 12 yr before attending the clinic. The patients lacking medical follow-up were older than those with medical follow-up (37.5 vs. 28.2 yr, $P < 0.01$) and mean time since diagnosis was longer (26.7 vs. 17.0 , $P < 0.01$).

TABLE 1. Patient characteristics (n = 150)

	Mean (sd) or %
Physical examination [mean (sd)]	
Age (yr)	31.0 (10.4)
Height (cm)	153.2 (7.5)
Weight (kg)	61.6 (13.6)
BMI (kg/m ²) ^a	26.2 (5.5)
Karyotype (%)	
45,X	47
45,X/46,XX ^b	12
45,X/47,XXX	3
45,X/46,X,i(Xq)	14
45,X/46,X,del(X)	5
45,X/46,XY or marker Y	3
45,X/46,X,r(X)	3
46,X,i(Xq)	3
46,X,del(X)	2
Others ^c	5
Pending ^d	3
Medical care before investigation (%)	
Direct transition from pediatric care	17
Specialist care ^e	53
Gynecologist	36
Internist	7
Cardiologist	2
Combination of more than one specialist	8
No medical care	30

^a No difference in patients with and without diabetes.

^b Including one patient with mosaicism trisomie 21 as well.

^c Four patients with a mosaicism containing more than two cell lines, two patients with a marker chromosome, and two patients with a translocation with chromosome 13.

^d Patients were diagnosed with TS elsewhere; confirmation in our laboratory is pending.

^e Of these patients 6 had lacked medical attention during a mean period of 18.5 yr earlier in life.

TABLE 2. Screening protocol for adults with TS [adapted from Bondy (5), Saenger *et al.* (6), Conway (7)]

Investigation	Once	Every 1–2 yr ^a	Every 3–5 yr ^a
Height, weight, blood pressure, auscultation of the heart		X	
Creatinine, blood urea nitrogen, ASAT, γ -GT, TSH, fT ₄ , total cholesterol, low-density cholesterol, high-density cholesterol, triglycerides, glucose, HbA1c, urine dipstick analysis		X	
Celiac serology ^b			X
Karyotype	X		
Renal ultrasound	X		
Pelvic ultrasound	X		
Audiogram ^c	X		
Cardiac ultrasound, including electrocardiogram			X
MRI aorta (thoracic and abdominal)			X
Bone mineral density measurement (DEXA)			X

ASAT, Aspartate-aminotransferase; fT₄, free T₄; γ -GT, γ -glutamyl transpeptidase; HbA1c, glycated hemoglobin.

^a Frequencies are increased when abnormalities are found.

^b IgA antibodies to tissue transglutaminase and endomysium; in case of IgA deficiency, IgG antibodies were measured.

^c Repeat at age of 40.

Screening

All patients underwent a standardized medical evaluation adapted from expert opinion recommendations (5–7), which consisted of consultation (history and physical) by an endocrinologist, gynecologist, cardiologist, otorhinolaryngologist, and, in a selected group of patients, a psychologist. The work-up included laboratory investigations and imaging, as indicated in Table 2. Magnetic resonance imaging (MRI) scans were performed using Avanto 1.5T (Siemens, Erlangen, Germany). The protocol consists of dark blood (TSE db T1) and TRUFI images. Diameters of the aorta were measured at the level of the sinuses of Valsalva, the right pulmonary artery, the origin of the left subclavian artery, the left atrium, the diaphragm, the kidney arteries, and just above the bifurcation of the abdominal aorta. Also, the largest cross-sectional diameters of the thoracic and abdominal aorta were measured.

Echocardiographic evaluation was performed according to the American Society of Echocardiography recommendations (13). All examinations were performed by the same clinician (J.T.), using the echocardiography machine Vivid 7 or System Five (GE-Vingmed, Horten, Norway) connected to a phased-array probe (2.5 and 3.5 MHz). Digitized measurements of the aortic root were made in two-dimensional parasternal long-axis views at end-diastole using the leading-edge technique at four aortic levels: the annulus, the sinuses of Valsalva, the supraaortic ridge, and the proximal ascending aorta. The largest aortic diameter obtained in these views was described.

A 12-lead electrocardiogram (ECG) was performed to diagnose conduction or repolarization abnormalities.

Bone mineral density was measured at the lumbar spine (L1–L4) and the right femoral neck using a QDR 4500 densitometer (Hologic, Zaventem, Belgium). Bone mineral density was expressed as T- and Z-scores based on a normal reference population.

Standard renal ultrasound was performed for assessment of morphological abnormalities.

Hearing measurements were conducted according to standard audiometric methods (ISO 389) in a soundproof room. Air conduction thresholds were measured in decibel hearing level at 0.25, 0.5, 1, 2, 4, and 8 kHz and bone conduction thresholds were measured in decibel hearing level at 0.5, 1, 2, 4, and 8 kHz.

Data analysis and statistics

The analysis was restricted to the findings of the initial evaluation. No data of subsequent follow-up visits are presented. We recorded all newly identified diagnoses. In case of previous diagnoses, relevant changes in treatment were recorded. Case finding definitions are given in Table 3. For individual patients, TS-related disease burden was calculated as the total number of diagnoses among the following principal stigmata (maximum score of 14): bicuspid aortic valve, coarctation of the aorta, elongation of the transverse aortic arch, dilation of the aorta, diabetes, glucose intolerance, hypertension, dyslipidemia, osteoporosis or osteopenia, (subclinical) hypothyroidism, celiac disease, renal anomalies, liver enzyme disturbances, and hearing loss requiring a hearing aid (14). Results are expressed as mean (SD), unless mentioned otherwise. To analyze which patients benefit most from the standardized screening, we performed a subgroup analysis and compared the yield of diagnoses between patients with different times since initial diagnosis, patients with or without previous care, and patients with monosomy 45,X *vs.* patients with other karyotypes. For subgroup analyses and comparisons of means, Student's *t* test or χ^2 tests were used where appropriate. We used Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, IL).

Data were collected under conditions of regular clinical care, with institutional review board approval obtained for the use of these data for scientific reasons.

Results

New diagnoses and total prevalence of morbidity are summarized in Table 4 and Fig. 1. The disease burden in individual patients was 1.2 ± 1.2 diagnoses before screening and 3.5 ± 1.9 diagnoses after screening ($P < 0.01$). The mean increase in disease burden was 2.3 ± 1.5 . When comparing patients with 45,X with those with other karyotypes, the former had a disease burden of 3.7 ± 1.8 diagnoses after screening and the latter 3.3 ± 2.0 . Patients with 45,X had significantly more new diagnoses during

TABLE 3. Case finding definitions

	Case finding definition
Congenital anomalies of the heart/aorta	Bicuspid aortic valve, coarctation of the aorta, elongation of the transverse aortic arch
Dilation of the aorta	Dilation of the ascending aorta based on BSA corrected values (17, 40) and/or local or fusiform dilation of the descending aorta
Diabetes	Diabetes: random glucose >11.1 mmol/liter or HbA1c \geq 6.5 mmol/liter Impaired glucose tolerance: random glucose between 7.8 and 11.1 mmol/liter or HbA1c between 5.7 and 6.4% (41)
Hypertension	Use of antihypertensive medication or systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg
Dyslipidemia	TC \geq 5.50 mmol/liter and/or HDL-C \leq 1.10 mmol/liter and/or LDL-C \geq 3.50 mmol/liter and/or TG \geq 2.20 mmol/liter (random lipid profiles)
Diminished bone mineral density	Osteoporosis: T-score \leq -2.5 sd; osteopenia: T-score between the -1.0 and -2.5 sd
Hypothyroidism	Hypothyroidism: TSH above upper reference limit of 4.0 mEq/liter and fT ₄ below lower reference limit of 8.0 pmol/liter Subclinical hypothyroidism: TSH >4.0 mEq/liter and fT ₄ within normal range (8.0–22.0 pmol/liter)
Structural anomalies of the kidney	Horseshoe kidney, duplication of the collecting system, agenesis, and rotation as TS-specific renal malformations
Liver enzyme elevation	g-GT >35 U/liter and/or ASAT >40 U/liter

ASAT, Aspartate-aminotransferase; fT₄, free T₄; γ -GT, γ -glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

screening when compared with patients with other karyotypes (2.6 ± 1.5 vs. 2.0 ± 1.5). Age correlated positively with the disease burden before screening ($r = 0.485$) and after screening ($r = 0.689$) and the number of new diagnoses during screening ($r = 0.403$).

Anomalies of the heart and aorta

Before the current investigations, 81 patients (54%) had undergone cardiac ultrasound and 16 (10.7%) MRI. Eighteen had a previous diagnosis of structural cardiac and/or aortic anomalies. Five had undergone surgery. Re-

evaluation yielded additional aortic anomalies in six. Screening of 132 patients without previously known cardiac or aortic anomalies consisted of MRI and cardiac ultrasound ($n = 100$), MRI only ($n = 12$), and ultrasound only ($n = 9$). MRI results are pending in nine. In addition, MRI was not performed in six because of claustrophobia and in five because of recent cardiovascular screening including MRI. This yielded one or more congenital anomalies in 40 patients (30.3%). Fifteen of these patients had an additional dilation of the aorta. In 15 other patients, aortic dilation was an isolated finding. In the group with new discovered cardiac and aortic abnormalities ($n = 55$), 25 had previously undergone cardiac screening by cardiac ultrasound and MRI in one. In five patients, a bicuspid aortic valve was missed by previous screening. All other new diagnoses were attributable to screening with an additional MRI: elongation, mild coarctation, and dilation of the aorta. See Fig. 2 for images.

In women with karyotype 45,X, significantly more structural cardiovascular abnormalities were diagnosed compared with women with other karyotypes (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). Furthermore, the time since the initial diagnosis of TS correlated positively with a higher number of newly diagnosed structural cardiovascular abnormalities. (Supplemental Table 2).

An ECG was performed in 134 patients. All patients showed a sinus rhythm, including eight patients with sinus tachycardia (>100 beats per minute) and one with sinus bradycardia (<60 beats per minute). In 53.4% of the patients, the ECG was normal, 37.3% showed repolarization abnormalities (STT abnormalities), 17.2% QTc prolongation, 4.5% other conduction abnormalities, 3.0% left axis deviation, and 0.7% right axis deviation.

Concerning the diastolic and systolic function, we found that 2.0% of the women ($n = 3$) had an impaired cardiac function; one patient had an ejection fraction of 43.8%, and two patients had a dilated right ventricle, one due to an atrium septum defect and one due to a partial anomalous pulmonary venous return. We found one patient with left ventricular hypertrophy secondary to a bicuspid aortic valve with stenosis (15).

Atherosclerosis and risk factors

Two patients had a history of myocardial infarction at 31 and 44 yr of age. Seventeen patients (11.3%) were current smokers. Mean body mass index (BMI) was 26.2 ± 5.5 kg/m² (52.7% had a BMI >25 kg/m²; 20.7% had a BMI >30 kg/m²).

Seven patients were previously diagnosed with diabetes (four insulin dependent) and two with impaired glucose intolerance. No new cases of diabetes were encountered.

TABLE 4. TS-associated morbidity (n = 150)

	Previous diagnoses (n)	Changes in treatment (n)	New diagnoses (n)	Observed frequency (%)	Frequency literature (%) (3–5, 11, 17, 23, 24, 26, 27, 34, 38, 42, 43)
Bicuspid aortic valve	12	0	10	19 ^a	14–34
Aortic coarctation	2	0	6	9 ^a	7–14
Bicuspid valve and coarctation	3	0	4 ^b		
Elongation of the transverse aortic arch	0	0	27	18 ^a	~50
Dilation of the aorta	4 ^c	0	34	25 ^a	3–42
Diabetes type 1	2	0	0	1	0.5–5
Diabetes type 2	5	0	0	3	3–25
Glucose intolerance	2	0	12	9	7–50
Hypertension	17	5	39 ^d	37	24–50
Dyslipidemia	8	0	52	40	37–50
Osteoporosis	10		8	12 ^e	
Osteopenia	22		56	52 ^e	
Osteoporosis or osteopenia	32	4	64	64 ^e	50–80
Hypothyroidism	17	11	0	11	16–30
Subclinical hypothyroidism	7	2	33 ^f	27	
Celiac disease	0	0	3	2	4–6
Renal anomalies	23 ^g	0	7 ^h	20 ⁱ	28–38
Liver enzyme disturbances	5	0	45 ^j	33	36–80
Hearing loss requiring aid	31	1	8 ^k	26 ^l	27–44

^a Possible underestimation because of cardiac ultrasound in all, in 20 no MRI.

^b Including one recoarctation of the aorta.

^c Three in patients with a bicuspid aortic valve and/or coarctation.

^d Seven warranting medication.

^e Possible underestimation because of bone mineral density measurement in 146 patients.

^f Five warranting medication.

^g Horseshoe kidney (n = 15), duplication of the collecting system (n = 5), unilateral renal agenesis (n = 2), and malrotation (n = 1).

^h Horseshoe kidney (n = 3), duplication of the collecting system (n = 4).

ⁱ Possible underestimation because of renal ultrasound in 142.

^j Forty-six patients had a mild elevation of γ -glutamyl transpeptidase and/or aspartate-aminotransferase (ASAT). ASAT was below twice the upper limit in all cases.

^k Additional 35 with hearing impairment.

^l Possible underestimation because of ear, nose, and throat consult in 110 patients.

Seventeen patients were known with hypertension, 10 of whom had insufficient blood pressure control. An additional 39 patients had an elevated blood pressure based on supine office sphygmomanometric measurements at time of consultation. In the context of individual cardiovascular risk, medication was started in seven.

Eight patients were previously diagnosed with dyslipidemia, and three of them were currently taking a statin. In the others, lipid profile was abnormal in 36.6%.

Fertility and HRT

In 36 patients, spontaneous menarche had occurred. In the remaining 114 patients, puberty was induced by estrogen therapy in 107. In three patients with 45,X, fertility treatment with egg donation resulted in one successful pregnancy. Spontaneous pregnancies occurred in two patients with mosaicism. Two other patients with mosaicism attempted to become pregnant with fertility treatment,

one including egg donation, but did not succeed. Five patients were known with a (partial) Y chromosome. Prophylactic gonadectomy took place except in two; one refused, and in the other, the *SRY* gene was absent.

Gynecological ultrasound in 117 patients revealed a uterus subseptus in two, a uterine myoma in two, and a polyp in one.

At referral, 146 women were below 52 yr of age, the median age for menopause. In this group, 23 women lacked any form of HRT, including seven with a spontaneous menstrual cycle and one because of current fertility treatment.

The different regimes of the 124 (one above 52 yr of age) patients already on HRT were continuous combined (15.3%), sequential combined (54.0%), oral contraceptives (28.2%), and estrogen only (2.4%). Eight of them previously lacked HRT for a mean duration of 6 yr. In 31

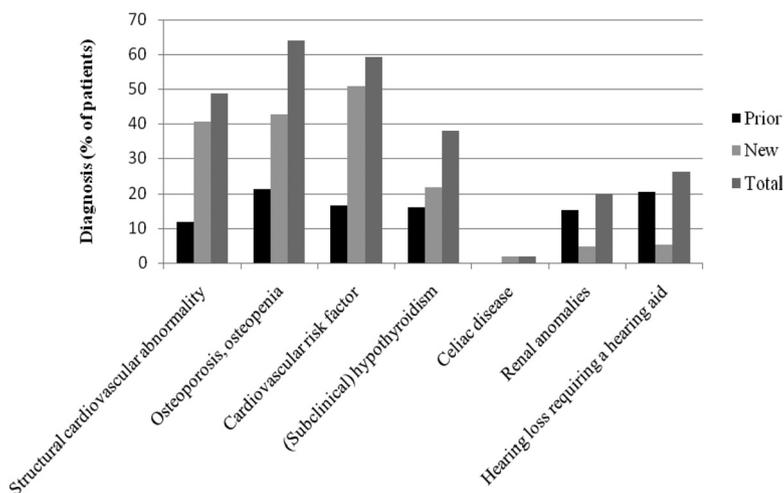


FIG. 1. Frequencies of TS-associated morbidities in 150 TS patients.

patients, the regimen was intensified or otherwise adjusted because of decreased bone mineral density ($n = 5$), metrorrhagia, dysmenorrhea, and/or the patient's preference to switch to a noncyclic regimen ($n = 26$).

Bone mineral density

Forty-six patients (30.7%) had a history of trauma-associated fractures. Forty-three patients (28.7%) had previously undergone a bone mineral densitometry, yielding osteoporosis in 10 and osteopenia in 22. Ten of these patients were taking bisphosphonates. Based on 26 repeated bone mineral density measurements, four patients needed adjustment of therapy. In 118 patients without a previous diagnosis, 111 bone mineral density measurements were performed. In patients with osteoporosis ($n = 8$) or osteopenia ($n = 56$), lifestyle interventions enhancing bone health were advocated, *i.e.* adequate calcium intake, exposure to sunlight, and weight-bearing exercise. Additionally, HRT was started or intensified in eight, calcium/vitamin D supplementation was started in eight, bisphosphonates were prescribed in two, and a combination of calcium/vitamin D supplementation and change in HRT occurred in two.

Thyroid disease

Seventeen patients had a history of hypothyroidism and were taking thyroid hormone. The dose needed adjustment in 11 patients. We found 33 cases of new subclinical hypothyroidism, prompting supplementation of thyroid hormone in five symptomatic cases.

Kidney malformations

Seventy-two patients (48%) had previously undergone renal ultrasound showing anomalies in 23 patients. Three patients had undergone surgical interventions.

Of the remaining 78 patients, 70 underwent a renal ultrasound yielding anomalies in seven. Renal function

was normal in all patients. Isolated erythrocyturia was found in two patients without structural anomalies or proteinuria. In eight patients, renal ultrasound results are pending.

Hearing loss

Thirty-one patients already had a hearing aid, including four patients with a bone-anchored hearing aid. Of 119 without a previous diagnosis, 78 underwent audiology indicating significant hearing impairment in 43 patients, with the requirement of a hearing aid in eight.

Psychological problems

Twenty-three patients (mean age 38 yr) consulted the psychologist with the following reasons: need for support in accepting TS-related limitations in daily life (70%), low self-esteem (55%), nonassertiveness (45%), lack of social support (25%), and infertility-related emotional problems (10%).

Abnormalities regarding celiac disease and liver enzyme disturbances are specified in Table 4.

When comparing the women without previous medical care and the women with adult specialist care to the women with direct transition from pediatric care we found that a larger number of new diagnoses were found in the first group (Table 5).

Discussion

We investigated the yield of comprehensive screening for TS-associated morbidity in a large group of adult TS patients in a single Dutch center. Multidisciplinary evaluation identified many patients with previously unknown diagnoses, including cardio-aortic anomalies (40.7%), hypertension (26.0%), dyslipidemia (34.7%), impaired glucose tolerance (8.0%), current or previous lack of HRT despite estrogen deficiency (15.3%), osteoporosis (5.3%), osteopenia (37.3%), subclinical hypothyroidism (22.0%), and hearing loss requiring a hearing aid (5.3%). In individual patients, on average, two new major TS-related diagnoses were found. Patients without previous specialist care benefited most from the screening.

In the majority of patients, 76% in our cohort, TS was diagnosed in childhood triggered by dysmorphic features, impaired growth, and/or delayed puberty. Ensuing GH treatment and induction of puberty requires strict pediatric follow-up. Many patients are lost to follow-up after discharge from pediatric care (8–11). In the present cohort, one third lacked any form of ongoing specialist care. Lack of care was most prevalent among older patients. It is unclear which patients are prone to lack ongoing med-



FIG. 2. MRI and MRA images of anomalies of the heart and aorta. A, Coarctation of the aorta; B, dilation of the aorta; C, bicuspid aortic valve; D, elongation of the transverse aortic arch. [Reproduced with permission from K. Freriks *et al.*: *Ned Tijdschr Geneesk* 151:1616–1622, 2007 (44) © Nederlands Tijdschrift voor Geneeskunde.]

ical care. It might be that socioeconomic factors play a role. We have insufficient data to investigate this. However, in The Netherlands, health insurance is obligatory by law and entitles all patients to identical care.

The importance of a well-organized transition from pediatric to adult care was stressed by the Turner Syndrome Consensus Study Group (5). Besides a well-organized transition, a multidisciplinary periodic screening of adult women with TS is advocated in international expert-based guidelines, mainly because many disorders do not present

until adult age (5–7). Our current finding of a significant previously unrecognized morbidity demonstrates the effectiveness of such an approach.

Medical care in adult women with TS is mainly aimed at reduction of the approximately 3-fold increase in age-related risk of cardiovascular mortality (2). The necessary screening for structural cardiac and aortic anomalies had been omitted in half of our patients. Current screening revealed unknown cardiac and/or aortic anomalies in approximately 40% of the patients. Cardio-aortic anomalies and hypertension are assumed to increase the risk of aorta dilation and dissection (4, 16, 17). The prevalence of aortic dilation increases with age, but dilation in TS can already be present in the second decade of life (18, 19). Aortic dissection occurs at relatively young age (third decade) with an age-dependent incidence of 15–50 cases in 100,000 TS years compared with six cases in the normal population (20). Considering the fact that aortic abnormalities are usually asymptomatic until complications occur, periodic screening of the aortic diameter appears to be justified. Cardiac follow-up can be performed using ultrasound and MRI, the latter having the advantage of superior imaging of the coarctation site and the distal aorta (16, 19). In a recent report, Matura *et al.* (17) advise to use aorta size index (aortic diameter/body surface area) instead of absolute aortic diameter because of limited

availability of reference values for aortic diameters. The authors suggest strict follow-up in case of an aorta size index of at least 2.0 cm² and evaluation for prophylactic intervention in case of an aorta size index of at least 2.5 cm² in combination with an absolute aorta diameter above 3.5 cm. In (induced) pregnancy, the risk of dissection is even higher, and in one retrospective study, the pregnancy-related mortality is estimated at 2% (21). Cardiovascular screening is strongly advised before and dur-

TABLE 5. Impact of previous care on percentage of new diagnoses

	Direct transition from pediatric care (mean age 19.0 ± 1.5 yr)	Preceding adult specialist care (mean age 31.3 ± 9.1 yr)	No specialist care (mean age 37.5 ± 9.2 yr)
Structural cardiovascular abnormalities (%)	34.6	31.7	60.0 ^a
Osteoporosis or osteopenia (%)	53.9	32.9 ^a	53.3
Cardiovascular risk factors (%)	34.6	51.9	57.8 ^a
(Subclinical) hypothyroidism (%)	15.4	15.2	37.8 ^a

^a Significant compared with women directly referred from pediatric care.

ing each pregnancy. In fact, pregnancy is discouraged in patients with congenital cardiac and aortic anomalies, hypertension and/or an aortic size index (aortic diameter/body surface area) of at least 2.0 cm/m² (22).

Besides structural anomalies, TS in adults is associated with an unfavorable risk profile for cardiovascular disease. The prevalence of atherosclerosis is doubled (23). In the present young population, 37% had hypertension, 40% had an abnormal nonfasting lipid profile, 5% had diabetes, and half of the patients were overweight. Prevalence of diabetes type 2 in the TS population is increased compared with the general population. Focusing on the age group around 30, incidence numbers vary. Bakalov *et al.* (24) found a prevalence of diabetes type 2 in 25% of a young TS population (age 35.4 ± 11.3 yr, BMI 28.9 ± 7.7 kg/m²), whereas Landin-Wilhelmsen *et al.* (25) reported a prevalence of 3% in a similar age group (age 33.7 ± 11 yr, mean BMI 25.9 ± 5.0 kg/m²). Probably this difference is related to differences in BMI. Nevertheless, the clearly unfavorable cardiovascular risk profile at young age suggests that patients benefit from screening and careful management. Intervention trials, however, are lacking.

The pathophysiology of the increased prevalence of autoimmune disease, especially in association with Xi(Xq) genotypes, remains unknown. We confirm a high prevalence (38%) of hypothyroidism, including subclinical cases. Previous studies have indicated that 16–30% of the TS patients have elevated TSH levels and that 27–45% of the TS patients have positive thyroid antibody titers (26, 27). Furthermore, we found three patients with proven celiac disease. It has been shown that celiac disease is more common in the TS population with a prevalence of 4–6% (28). Ongoing periodic screening for both hypothyroidism and celiac disease seems reasonable because incidences increase with age. Vigilance for additional less common TS-related autoimmune diseases is essential (28–30).

Another important issue that needs ongoing medical attention, at least until normal age of menopause, is HRT. HRT in estrogen-deficient women has a positive effect on bone mineral density, prevents vaginal atrophy, and was shown to have a favorable impact on cardiovascular risk in TS (31). In our cohort, 15% lacked HRT, which is similar to observations in other countries (9, 32). In about half of the cases, HRT was discontinued by the patient because of self-reported side effects or unawareness of the reasons for HRT. In others, HRT was never started. One reason could be that physicians might be unjustly reserved regarding HRT because of the relationship with breast cancer in elderly postmenopausal women (33).

Two thirds of our TS patients were found to have a low bone mineral density correlated with older age and lack of HRT. TS is associated with an intrinsic structural bone

defect, which is worsened by estrogen deficiency (34). Because short stature can cause false low areal bone mineral density, it is possible that the high frequency of osteoporosis observed in TS patients based on bone mineral density measurements is in fact an overestimation (35). Nevertheless, a higher fracture risk in TS, varying from 24–32%, has been established, warranting careful observation and treatment of bone health, including optimal HRT (32, 36).

During childhood, the vast majority of TS patients suffer from recurrent glue ear, otitis media, and resulting conductive hearing loss, probably related to an abnormal Eustachian tube (37). During adulthood, conductive and perceptive hearing loss frequently occurs, the latter often with either a mid- or high-frequency dip. In our group, more than 25% of patients suffered from significant hearing impairment warranting the use of a hearing aid, which is similar to previous reports. Hultcrantz (38) found that 27% of TS patients needed a hearing aid (n = 324; age range 4–68) and as many as 44% when focusing on those aged above 35 yr.

Besides physical health issues, women with TS often deal with (neuro)psychological problems (39). Our study confirms that many TS women experience difficulties in regard to acceptance of limitations related to TS and low self-esteem. Remarkably, emotional problems related to infertility were mentioned by only a small minority.

In conclusion, standardized multidisciplinary evaluation of adult women with TS yields significant previously undiagnosed morbidity. TS patients are therefore likely to benefit from a careful transition from pediatric into adult medical care, consisting of a multidisciplinary service with standardized screening for TS-associated morbidity. To what level our approach improves long-term morbidity, mortality, and health-related quality of life remains to be investigated. The actual benefit should also be weighed against the costs of screening and the risk of medicalization.

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