Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(1): 22
https://doi.org/10.31083/j.ceog5001022

Original Research

Challenges of Turner Syndrome Care in Adulthood: A Single Tertiary Center Experience

Ralitsa Robeva[1,*], Atanaska Elenkova[1], Sabina Zacharieva[1]

[1]Department of Endocrinology, Medical Faculty, Medical University-Sofia, USHATE "Acad. Iv. Penchev", 1431 Sofia, Bulgaria
*Correspondence: rali_robeva@yahoo.com (Ralitsa Robeva)
Academic Editor: Panagiotis Anagnostis
Submitted: 25 August 2022 Revised: 13 November 2022 Accepted: 16 November 2022 Published: 16 January 2023

Abstract

Background: Turner syndrome (TS) is a well-known genetic condition associated with increased morbidity and mortality in adult patients. Accordingly, comprehensive guidelines for TS follow-up across the lifespan have been developed. However, the data about their implementation in clinical practice need to be expanded. The present study aims to describe a cohort of adult East-European TS patients and to highlight pitfalls in long-term medical care. **Methods**: Data from 45 TS women (18–53 years) were included in the present retrospective study. Personal history of the patients along with anthropometric, cytogenetic, clinical, and laboratory parameters were collected. **Results**: The median age of initial diagnosis was 15 years varying between one and forty-nine years, with nearly one-third of patients being diagnosed as adults. TS women treated with growth hormone during childhood were, on average, 5 cm taller than the non-treated patients (150.00 [147.00–155.00] *vs*. 145.00 [140.25–150.75], $p = 0.055$). Patients on hormone replacement therapy (HRT) had higher high density lipoprotein (HDL) cholesterol levels (1.80 mmol/L [1.44–1.99] *vs*. 1.55 mmol/L [1.31–1.74], $p = 0.041$) and lower follicle-stimulating hormone levels (33.70 IU/L [23.65 – 65.07] *vs*. 70.00 IU/L [46.90–79.39], $p = 0.008$) compared to non-treated women. Adherence to HRT was suboptimal, with only 55.6% of hypogonadal women being on hormonal treatment. The presence of comorbidities was increased as expected, but the percentage of hypertensive TS patients was lower than usually reported (11.1%). **Conclusions**: Growth hormone and estrogen replacement therapy might exert different positive effects on TS patients. However, the late diagnosis of TS and low adherence to treatment could limit the beneficial hormonal effects. A tendency for a more accurate diagnosis of concomitant endocrine diseases compared to non-endocrine conditions in TS patients has been observed. These results support the need for dedicated multidisciplinary teams focused on TS diagnosis and adult follow-up worldwide.

Keywords: Turner syndrome; hypogonadism; disorders/differences in sex development (DSD); growth hormone therapy

1. Introduction

Turner syndrome (TS) is a well-known sex chromosome disorder/difference in sex development characterized by premature ovarian failure with hypoestrogenism, short stature, specific physical features, and increased prevalence of comorbidities [1–3]. Total or partial loss and structural abnormalities of the second X chromosome in phenotypic females may be associated with variable severity of clinical manifestations; therefore, TS might be diagnosed at different stages of the lifespan [4]. Typically, patients with TS are diagnosed in childhood and receive complex medical care in pediatric settings per evidence-based recommendations [3–5]. However, the transition to adult healthcare services is often associated with different hurdles, such as a lack of a multidisciplinary approach, insufficient evidence for the optimal treatment regimens, as well as significantly reduced financial reimbursement of medical consultations and investigations by local health insurance funds for older women in comparison to children [6]. Additionally, some patients are diagnosed with TS as adults, leading to delayed hormonal treatment and possible long-term complications [7,8].

The main objectives of medical care in TS children and adolescents are growth improvement by growth hormone treatment (GHT) and puberty induction [4,5]. In adulthood, major priorities include maintenance of hormone-replacement therapy (HRT), counseling about fertility and available assisted reproductive technologies, and early identification and treatment of concomitant diseases [4,5]. TS is associated with an increased prevalence of cardiovascular, renal, gastrointestinal, metabolic, and autoimmune disorders leading to increased mortality [4,5]. One of the significant threats in TS women is fatal aortic dissection or rupture, which could affect relatively young patients, especially in the presence of underlying risk factors such as aortic abnormalities or hypertension [3]. The proper estimation of disease burden in TS is possible only by targeted standardized multidisciplinary evaluation; otherwise, many disorders would be omitted [9].

In recent years, comprehensive guidelines for holistic adult care have been developed [4,10]. However, most pieces of evidence emerge from a few European countries with national registers, such as Denmark, Sweden, and the UK [10]. Conversely, data about adult TS care in other countries are insufficient.

Accordingly, the present study aims to describe a cohort of adult East-European TS patients and to highlight pitfalls in long-term medical care.

2. Methods

2.1 Patients and Study Parameters

Adult patients with Turner syndrome (TS) who had been consulted consecutively in a single tertiary Endocrine department (USHATE "Acad. Iv. Penchev", Medical University-Sofia, Bulgaria) between 2002 and 2022 have been included in the present retrospective, cross-sectional study. Personal and family history of the patients along with anthropometric, cytogenetic, clinical, and laboratory parameters were extracted from the hospital's electronic database and/or paper files. Additionally, information about imaging studies, treatment regimens, and comorbidity of patients was collected from files generated at the first clinical visit. The hormone replacement therapy of TS patients included estradiol hemihydrate or ethinylestradiol in combination with different types of gestagens. Patients in the early stages of puberty induction received only estrogens.

Patients with clinical symptoms of TS without documented cytogenetic studies were considered ineligible for the study. Data from 45 TS female patients (18–53 years) were selected for the final analyses. Laboratory parameters (blood glucose, lipid profile, liver enzymes, creatinine, *etc*.) were measured enzymatically by an automatic analyzer (Cobas Mira Plus; Hoffmann La Roche), as shown previously [11]. Hypertension was defined as the presence of office systolic blood pressure $\geq$140, diastolic blood pressure $\geq$90, or already prescribed antihypertensive treatment.

Cytogenetic studies were performed in licensed genetic laboratories following national standards. Thyroid and abdominal ultrasounds were performed routinely in the Endocrine department. Since audiometry and echocardiography were not done routinely in the department for most of the period, data about concomitant cardiovascular and otological abnormalities were obtained from the patient's medical files based on the registered pathological findings. Magnetic resonance imaging is not routinely provided and reimbursed for TS patients according to local regulations, and only one patient had been referred by the cardiologist for magnetic resonance imaging of the heart, with no abnormal findings.

2.2 Statistical Analysis

Descriptive statistics and frequency analyses have been used to describe patients' characteristics. Additionally, χ^2 and Fisher's exact tests have been applied to analyze dichotomous variables. The distribution of most parameters differed from normal after a Kolmogorov-Smirnov test for normality. Therefore, non-parametric statistic tests have been used. Thus, all values are presented as median [interquartile range (IQR): Q1–Q3] or as frequency (%). Differences between the two groups have been established by a Mann-Whitney test. Similar results have been obtained by using parametric tests. A "*p*" level of 0.05 was considered statistically significant. Calculations were made with a MedCalc® Statistical Software version 20.110 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

3. Results

3.1 Anthropometric Characteristics, History, Age at Diagnosis, and Karyotype

The mean age of investigated patients was 24.00 years (IQR 19.0–31.25), varying between 18 and 53 years. The mean height was 148.00 cm (IQR 142.00–152.87 cm), while the mean weight was 52.00 kg (IQR 46.75–60.75). The mean body mass index (BMI) was 23.83 kg/m^2 (IQR 21.50–27.79), with 21 of the patients (46.2%) being overweight (BMI $\geq$25). The age of diagnosis varied widely between the neonatal and mature stages of lifespan, with a median of 15 years (IQR 12.0–19.0). More than one-third of patients were diagnosed in adulthood (16 patients [35.8%]), and the latest age at diagnosis was 49 years. A total of 25 patients (55.6%) carried monosomy 45, X, while the rest carried mosaic karyotypes with or without structural chromosome abnormalities. Monosomic 45, X patients had been diagnosed much earlier than patients with other karyotypes (14 years [IQR 10.75–17.00] *vs*. 19 years [IQR 14.00–23.50], p = 0.018). Four patients (8.9%) were carriers of the Y-cell line, three of whom were gonadectomized, while one patient diagnosed at the age of 19 refused the operation and subsequent follow-up. Two-thirds of patients (n = 30) demonstrated primary amenorrhea, while the rest (n = 15) complained of secondary amenorrhea. The median age of menarche in the second group had been 14 years (IQR 14.00–16.00 years); after that, the TS girls developed oligo- or amenorrhea. In adulthood, TS patients were amenorrheic with the hormonal constellation of hypergonadotropic hypogonadism. Primary amenorrhea was more common in monosomic patients compared to patients with mosaic karyotypes (22 of 25 patients (88%) *vs*. 8 of 20 patients (40%), p = 0.001). No pregnancies were observed, though some patients considered pregnancy by egg donation in the future.

3.2 Hormonal Treatment with Growth Hormone, Estrogens, and Progestins

Growth hormone therapy during childhood was provided to 40.0% of patients, regardless of the specific karyotype (Table 1). All patients discontinued growth hormone therapy at the age of 18 years, following national standards. Patients treated with growth hormone were, on average, 5 cm taller compared to non-treated patients (Table 1). Growth hormone therapy was provided only to patients diagnosed with TS at an early age. Therefore, the growth hormone-treated women were significantly younger than non-treated individuals, which corresponded to a better lipid profile.

Table 1. Differences in anthropometric and biochemical parameters according to the previous growth hormone (GH) treatment (up to 18 years).

	Patients without previous GH treatment		Patients on previous GH treatment		p^a
	n	Median [IQR: Q1–Q3]	n	Median [IQR: Q1–Q3]	
Age (year)	27	26.00 [20.00–37.50]	18	20.50 [18.00–25.00]	0.015
Age at diagnosis (year)	27	19.00 [15.00–23.75]	18	12.00 [5.00–14.00]	<0.001
45, X (%, n)	27	51.9% [n = 14]	18	61.1% [n = 11]	0.760[b]
Height (cm)	27	145,00 [140.25–150.75]	18	150.00 [147.00–155.00]	0.055
Weight (kg)	27	52.00 [48.50–63.75]	18	52.00 [44.00–59.00]	0.302
BMI (kg/m^2)	27	26.02 [22.00–28.47]	18	22.48 [20.55–25.78]	0.072
Erythrocytes ($\times 10^6$)	24	4.55 [4.25–4.90]	17	4.40 [4.25–4.70]	0.244
Leucocytes ($\times 10^6$)	24	6.70 [5.25–7.70]	17	6.40 [5.57–8.32]	0.947
Thrombocytes ($\times 10^6$)	23	278.00 [224.5–305.75]	17	248,00 [231.25–345.25]	0.880
Cholesterol (mmol/L)	22	5.26 [4.75–5.70]	16	4.24 [3.98–5.00]	0.001
HDL-cholesterol (mmol/L)	19	1.61 [1.31–1.79]	14	1.90 [1.66–2.15]	0.007
LDL-cholesterol (mmol/L)	18	3.34 [2.63–3.72]	14	2.13[1.58–2.69]	0.001
Triglycerides (mmol/L)	21	1.24 [0.82–1.36]	16	0.72 [0.60–0.85]	0.015
ALAT (IU/L)	22	18.10 [12.40–41.40]	14	16.85 [12.00–36.00]	0.685
ASAT (IU/L)	22	21.60 [17.60–28.40]	14	19.00 [17.00–24.00]	0.445
Glucose (mmol/L)	22	5.19 [4.70–5.52]	18	4.92 [4.50–5.34]	0.237
Creatinine (μmol/L)	21	48.00 [42.75–58.25]	16	50.00 [46.50–60.00]	0.471
HRT (%, n)	27	44.4% [n = 12]	18	72.2% [n = 13]	0.078[b]
FSH[c] (IU/L)	21	46.90 [27.17–70.27]	16	63.65 [33.00–77.80]	0.358

[a] Mann-Whitney test; [b] Fisher's exact test; [c] Obtained on different hormonal regimens.

IQR, interquartile range; BMI, body mass index; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; HRT, hormone replacement treatment; FSH, follicle-stimulating hormone.

Table 2. Prevalence of different concomitant diseases in patients with monosomic and mosaic TS.

Disease	Patients with TS	Monosomic TS	Mosaic TS	p^a
	n = 45	n = 25	n = 20	
	% (n)	% (n)	% (n)	
Age (years)[b]	24.00 [19.00–31.25]	23.00 [19.00–32.75]	25.00 [19.00–29.00]	0.671[c]
BMI (kg/m^2)[b]	23.83 [21.50–27.79]	22.98 [21.24–26.26]	26.14 [21.93–28.37]	0.120[c]
Prediabetes	11.1% (5)	20% (5)	0% (0)	0.056
DM type 2	6.6% (3)	4% (1)	10% (2)	0.577
Arterial hypertension	11.1% (5)	16% (4)	5% (1)	0.362
Cardiovascular diseases	24.4% (11)	40% (10)	5% (1)	0.012
Gastro-intestinal and liver diseases	17.8% (8)	16% (4)	20% (4)	1.000
Neurological diseases	15.6% (7)	16% (4)	15% (3)	1.000
Nephrological diseases	20.0% (9)	24% (6)	15% (3)	0.709
Hashimoto's thyroiditis	55.6% (25)	60% (15)	50% (10)	0.557
Hypothyroidism (on L-T4 treatment)	20.0% (9)	16% (4)	25% (5)	0.481

[a] Fisher's exact test; [b] Data presented as median (interquartile range: Q1–Q3); [c] Mann-Whitney test.

TS, Turner syndrome; BMI, body mass index; DM, diabetes mellitus; L-T4, levothyroxine.

Thirteen patients (28.9%) were newly diagnosed with TS in the department because of primary or secondary amenorrhea. Other women with known TS were referred to the clinic by adult specialists in primary care or transferred from the pediatric endocrinology services after reaching the age of 18 years. Nevertheless, just over half of the patients were on systemic hormonal treatment for their apparent hypogonadism at the time of their first visit to the Endocrine department, while the remaining 44.4% (n = 20) had not begun or had discontinued hormonal treatment. Two patients discontinued hormone-replacement therapy because of medical specialist advice (one because of mammary fibroadenoma and the other because of pancreatitis). Additionally, one patient refused treatment because of subjective

side effects; however, the remaining patients did not report any specific reasons for discontinuation of therapy.

Patients on estrogen therapy with or without progestin had higher high density lipoprotein (HDL)-cholesterol levels (1.80 mmol/L [1.44–1.99] *vs.* 1.55 mmol/L [1.31–1.74], $p = 0.041$) and lower FSH levels (33.70 IU/L [23.65–65.07] *vs.* 70.00 IU/L [46.90–79.39], $p = 0.008$) compared to non-treated patients, despite the similar age and BMI of both groups ($p > 0.05$). No other significant differences in glucose, creatinine, low density lipoprotein (LDL)-cholesterol, triglycerides, or liver enzyme levels were observed ($p > 0.05$ for all).

Twenty-four percent (n = 6) of patients on hormonal medication were still on estrogen-only therapy because of the recent induction of pubertal development, while the remaining 20% (n = 5) received oral contraceptives, and 56% (n = 14) were on combined hormone-replacement therapy. Only 8% (n = 2) of patients used transdermal treatment, while all the others were on oral medications.

3.3 Concomitant Endocrine and Non-Endocrine Diseases

The prevalence of different concomitant diseases in patients with monosomic or mosaic TS was compared (Table 2). Carbohydrate disturbances (prediabetes or diabetes mellitus (DM)) were found in 24% (n = 6) of monosomic and in 15% (n = 3) of mosaic TS patients ($p = 0.709$); only one of the patients (with mosaic karyotype) presented as type 1 DM. Half of the investigated patients (n = 38) showed increased cholesterol levels regardless of the karyotype [monosomic 50% (n = 19) *vs.* mosaic 50% (n = 19), $p = 1.000$]. Cardiovascular diseases were found in approximately one-quarter of the patients, predominantly affecting monosomic women. Arterial hypertension was diagnosed in one-tenth of all cases (Table 2). Cardiovascular anomalies included different valve abnormalities (bicuspid aortic valve, n = 2; aortic dilatation, n = 2; aortic stenosis, n = 3; and other valve abnormalities, n = 3) as well as electrophysiological disturbances, e.g., right bundle branch block, supraventricular tachycardia (three patients, two with valve abnormalities).

Various gastrointestinal and liver diseases were found in TS patients: two patients suffered from congenital intestinal malformations, one from celiac disease, and one from duodenal ulcer. Three patients demonstrated hepatic steatosis, one was with pancreatitis, and one with cholelithiasis. One of the patients with steatosis showed strongly increased liver enzymes; additionally, seven patients had slightly increased transaminases. No significant differences in age (25.50 years [19.00–30.00] *vs.* 23.00 years [19.00–32.75], $p = 0.834$) or BMI (27.43 kg/m^2 [24.94–28.37] *vs.* 22.98 kg/m^2 [21.37–26.49], $p = 0.063$) were found between patients with increased liver transaminases and other TS women.

Nephrological disturbances (renal agenesis or dystopia, nephrolithiasis, *etc.*) were found in 20% of patients. Additionally, 15% of patients had a wide range of neuro-psychiatric conditions such as neurinoma, meningioma, epilepsy, and depression. One of the mosaic TS patients suffered from diabetes insipidus. Additionally, two patients complained of partial deafness (Table 2).

Autoimmune thyroid disease was diagnosed in more than half of the TS women, with over one-third already hypothyroid and on continuous levothyroxine treatment (Table 2). Thyrotoxicosis was found in only one patient with monosomic TS. Benign diseases of mammary glands were reported by three patients (6.67%). None of the patients suffered from any oncological illness. Only 19 patients had available data about bone density status. According to medical files, three women presented with already established osteoporosis, while in seven patients, the available dual-energy x-ray absorptiometry showed a lumbar spine Z-score below –2.0. Two patients showed a Z-score above 0; both had started appropriate hormone replacement therapy before 18 years of age and showed excellent adherence to treatment. No osteoporotic fractures had been reported by the patients.

4. Discussion

The presented results summarize the clinical characteristics of an adult TS patient group in a single tertiary East European endocrine center. More than one-third of patients were diagnosed as adults despite their short stature, pubertal delay, and additional symptoms. Most newly diagnosed adult women were referred for evaluation because of menstrual disturbances. At the same time, growth and additional symptoms were not considered as factors imposing the search for endocrinological help by some patients, especially in families where most members were of relatively short stature. Our results are in line with data from adult Indian patients diagnosed with TS because of amenorrhea in more than three-quarters of cases [12]. The evaluation of growth based on personal anthropometric data and parental height measurements may be a valuable tool for identifying abnormalities not only in children, but adults as well [13]. Thus, the auxological assessment should not be overlooked in routine adult endocrinological practice, as sometimes happens.

The median age of diagnosis of our TS cohort was 15 years, akin to those established in extensive population-based Danish studies [7,14] and, unsurprisingly, higher than those reported by pediatric investigations from the same and other countries [8,15]. Additionally, Bulgarian patients with 45, X monosomy had been diagnosed approximately five years earlier than patients with other karyotypes as in Denmark, despite the significant differences in socioeconomic status and health care organization of both countries [7,14].

Fifty-five percent of our patients demonstrated monosomic TS, a percentage slightly higher than expected based on the published prevalence. For instance, the prevalence

of 45, X karyotype was 32.1% in a recent study of pediatric TS patients of the same ethnic group [16]. Implementing prenatal screening programs in different countries, including ours, may account for decreased monosomic TS incidence because of a high rate of prenatal detection and induced abortions [14]. On the other hand, it might be assumed that a predominance of patients with prominent clinical features were referred to our tertiary center. Perhaps, the follow-up of mosaic TS individuals with milder symptoms was conducted by general practitioners, local endocrinologists, and gynecologists. The same suggestion could also explain the zero-fertility rate in our group, along with other factors, such as the financial and emotional burden of *in vitro* procedures.

According to our results, GHT has been associated with approximately 5 cm gain in final height. It should be emphasized that some of the treated TS individuals had started GHT with a substantial delay due to late diagnosis leading to suboptimal results. Therefore, the growth hormone effects in our cohort were slightly lower than those in other countries. The largest recent retrospective Brazilian study reported a mean height difference of 6.2 cm between non-treated TS patients and those treated with GHT for approximately five years on a standard dose [17]. A meta-analysis of nine randomized controlled trials using recombinant GHT concluded that treated TS girls were, on average, 7.2 cm taller than non-treated patients [18]. However, in international clinical practice, the final height gain varies widely between 2.10 cm and 10.69 cm, a gap attributable to different ages at initiation and duration of GHT, individual genetic features and adherence to therapy, as well as concomitant use of estrogens and oxandrolone [18–20].

Patients diagnosed with TS earlier than others tended to be on GH and estrogen treatment. The differences in mean age and estrogen use corresponded to a better lipid profile in GH-treated women compared to non-treated. Accordingly, Irzyniec *et al*. [21] found better lipid parameters in adult TS patients treated with GH during childhood compared to other TS women. In contrast to Polish data, the blood count characteristics, including thrombocytes and follicle-stimulating hormone levels, did not differ between the two investigated groups in our study. The early age of TS diagnosis leading to early GHT initiation has been considered a fundamental prerequisite for optimal GH effects [22]. However, other factors may also influence access and adherence to GH therapy and its efficiency, e.g., lower socioeconomic status, emotional issues, and poor understanding of drug therapy benefits and risks [23]. Thus, the positive influence of GHT in adulthood may reflect not only the biological effects of GH but also the healthier habits and nutrition and easier access to healthcare services of TS women with higher socioeconomic status.

Unfortunately, our results showed that 44% of hypogonadal TS patients at 18 years or above either had not started HRT or had discontinued it. The late TS diagnosis in amenorrheic women suggests that access to specialized endocrinological and/or gynecological consultations should be facilitated. On the other hand, the main factor associated with HRT self-discontinuation was not the development of absolute contraindications or lack of endocrinological evaluation but the poor understanding of therapy's importance. The percentage of estrogen-treated patients in our country was twice as low as in Denmark and Italy, where 83% to 92.5% of adult TS patients received HRT or oral contraceptives [24,25]. However, our data were similar to those reported by an Australian study showing a lack of hormonal treatment in 37% of adult TS patients [26]. The proper education of TS women about HRT benefits is the only way to ensure continuous adherence to therapy and to achieve the long-lasting positive effects of estrogens on bone, metabolism, and cognition [27]. As in other studies [1,24,25], bone density in half of the investigated women from our TS group was strongly decreased, corresponding to the low estrogen exposure. Current European guidelines recommend sufficient calcium intake, avoidance of vitamin D deficiency, and monitoring of bone density every five years in patients with TS or more frequently in case of estimated abnormalities [4,28]. HRT is needed until the physiological age of menopause not only for the prevention of bone loss but also for improving the cardiovascular and sexual health of TS women [4,28].

As expected, the evaluation of TS patients for concomitant diseases revealed a high prevalence of metabolic disturbances. Dyslipidemia was established in 50% of investigated patients, while overt DM type 2 was found in 6.6% of patients. The prevalence of DM type 2 was close to that reported by most studies (5%–10%) [4,26,29] but lower than that observed in the USA (25%) [30]. The prevalence of thyroid diseases and hypothyroidism in our cohort was similar to that of other European countries [1,31]. Cardiological and renal comorbidity distribution was close to expected [1,32]. Cardiological abnormalities were more prevalent in monosomic compared to mosaic patients, as in other studies [32,33].

In contrast, the established prevalence of hypertension (11%) was much lower than expected based on international reports, varying between 16% and 50% [1,25,29,34]. The high percentage of hypertension in TS patients has been associated with hypoestrogenism leading to increased sympathetic activity and with concomitant metabolic, cardiological, and/or renal abnormalities [35]. Ethnic and lifestyle peculiarities may explain the different prevalence of hypertension in distinct study cohorts, but increased blood pressure could also be underdiagnosed [35–37]. Our results strongly support current international recommendations suggesting ambulatory 24-h blood pressure monitoring in all adult TS patients at transition and at least once every five years after that to diagnose nocturnal hypertension [37,38].

5. Conclusions

In conclusion, our study confirmed that late diagnosis of TS in many patients leads to poor hormonal treatment. Moreover, the data showed the imperative for better education about evidence-based benefits and risks of HRT in young hypogonadal women. Diagnosis of concomitant endocrinological diseases in our TS patients, has been significantly more accurate compared to non-endocrine conditions. The main cause for the observed discrepancy is that TS patients' care has been provided primarily by local endocrinologists. These results support the worldwide need for dedicated multidisciplinary teams focused on TS diagnosis and follow-up in adulthood [5,6,39]. Additionally, the recommended laboratory investigations and imaging studies should be financially supported by local health insurance funds as a condition *sine qua non* to achieve a similar level of TS care in high-income and low-income countries.

Availability of Data and Materials

Datasets are available from the corresponding author on reasonable request after permission from the local authorities.

Author Contributions

RR—extraction, statistical analysis, and drafting of the manuscript; RR, AE, SZ—design, analysis of data, manuscript revision. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All subjects gave written informed consent permitting the research use of their pseudonymized data. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by USHATE "Acad. Iv Penchev" (approval number: 4/18.02.2019).

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Ralitsa Robeva is serving as one of the Guest editors of this journal. We declare that Ralitsa Robeva had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Panagiotis Anagnostis.

References

[1] Gravholt C. Epidemiological, endocrine and metabolic features in Turner syndrome. European Journal of Endocrinology. 2004; 151: 657–687.

[2] Orbañanos IR, Desojo AV, Martinez-Indart L, Bolado GG, Estevez AR, Echevarria IR. Turner syndrome: From birth to adulthood. Endocrinologia y Nutricion. 2015; 62: 499–506.

[3] Bondy CA. Care of Girls and Women with Turner Syndrome: a Guideline of the Turner Syndrome Study Group. The Journal of Clinical Endocrinology and Metabolism. 2007; 92: 10–25.

[4] Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, *et al*. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. European Journal of Endocrinology. 2017; 177: G1–G70.

[5] Elsheikh M, Dunger DB, Conway GS, Wass JAH. Turner's Syndrome in Adulthood. Endocrine Reviews. 2002; 23: 120–140.

[6] Shah S, Nguyen HH, Vincent AJ. Care of the adult woman with Turner syndrome. Climacteric. 2018; 21: 428–436.

[7] Stochholm K, Juul S, Juel K, Naeraa RW, Højbjerg Gravholt C. Prevalence, Incidence, Diagnostic Delay, and Mortality in Turner Syndrome. The Journal of Clinical Endocrinology and Metabolism. 2006; 91: 3897–3902.

[8] Apperley L, Das U, Ramakrishnan R, Dharmaraj P, Blair J, Didi M, *et al*. Mode of clinical presentation and delayed diagnosis of Turner syndrome: a single Centre UK study. International Journal of Pediatric Endocrinology. 2018; 2018: 4.

[9] Freriks K, Timmermans J, Beerendonk CCM, Verhaak CM, Netea-Maier RT, Otten BJ, *et al*. Standardized Multidisciplinary Evaluation Yields Significant Previously Undiagnosed Morbidity in Adult Women with Turner Syndrome. The Journal of Clinical Endocrinology and Metabolism. 2011; 96: E1517–E1526.

[10] Lin AE, Prakash SK, Andersen NH, Viuff MH, Levitsky LL, Rivera-Davila M, *et al*. Recognition and management of adults with Turner syndrome: from the transition of adolescence through the senior years. American Journal of Medical Genetics Part a. 2019; 179: 1987–2033.

[11] Robeva R, Elenkova A, Zacharieva S. Causes and Metabolic Consequences of Gynecomastia in Adult Patients. International Journal of Endocrinology. 2019; 2019: 6718761.

[12] Yadav Y, Saikia U, Sarma D. Delayed presentation of turner syndrome: Challenge to optimal management. Journal of Human Reproductive Sciences. 2017; 10: 297.

[13] Ouarezki Y, Cizmecioglu FM, Mansour C, Jones JH, Gault EJ, Mason A, *et al*. Measured parental height in Turner syndrome—a valuable but underused diagnostic tool. European Journal of Pediatrics. 2018; 177: 171–179.

[14] Berglund A, Viuff MH, Skakkebæk A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. Orphanet Journal of Rare Diseases. 2019; 14: 16.

[15] Stefanova E, Peneva L. Recombinant human growth hormone together with low dose estrogens stimulate growth and pubertal development in girls with Turner syndrome. Pediatria. 2010; 1: 49–53. (In Bulgarian)

[16] Rankova K, Iotova V, Mladenov W, Karamfilova T, Bazdarska Y, Yordanova N, *et al*. Treatment with recombinant growth hormone in children with Turner syndrome: a study from a tertiary university center. Scripta Scientifica Medica. 2021; 53: 9–14.

[17] Dantas NCB, Braz AF, Malaquias A, Lemos-Marini S, Arnhold IJP, Silveira ER, *et al*. Adult Height in 299 Patients with Turner Syndrome with or without Growth Hormone Therapy: Results and Literature Review. Hormone Research in Paediatrics. 2021; 94: 63–70.

[18] Li P, Cheng F, Xiu L. Height outcome of the recombinant human growth hormone treatment in Turner syndrome: a meta-analysis. Endocrine Connections. 2018; 7: 573–583.
[19] Dacou-Voutetakis C, Karavanaki-Karanassiou K, Petrou V, Georgopoulos N, Maniati-Christidi M, Mavrou A. The Growth Pattern and Final Height of Girls with Turner Syndrome with and without Human Growth Hormone Treatment. Pediatrics. 1998; 101: 663–668.
[20] Sánchez Marco SB, de Arriba Muñoz A, Ferrer Lozano M, Labarta Aizpún JI, Garagorri Otero JM. Human growth hormone and Turner syndrome. Anales De Pediatría. 2017; 86: 81–86. (In Spanish)
[21] Irzyniec T, Jeż W, Lepska K, Maciejewska-Paszek I, Frelich J. Childhood growth hormone treatment in women with Turner syndrome - benefits and adverse effects. Scientific Reports. 2019; 9: 15951.
[22] Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. Journal of Clinical Endocrinology & Metabolism. 2000; 85: 2439–2445.
[23] Fisher BG, Acerini CL. Understanding the Growth Hormone Therapy Adherence Paradigm: a Systematic Review. Hormone Research in Paediatrics. 2013; 79: 189–196.
[24] Gravholt CH, Vestergaard P, Hermann AP, Mosekilde L, Brixen K, Christiansen JS. Increased fracture rates in Turner's syndrome: a nationwide questionnaire survey. Clinical Endocrinology. 2003; 59: 89–96.
[25] Gambineri A, Scarano E, Rucci P, Perri A, Tamburrino F, Altieri P, *et al.* New insights into the comorbid conditions of Turner syndrome: results from a long-term monocentric cohort study. Journal of Endocrinological Investigation. 2022; 45: 2247–2256.
[26] Vincent AJ, Nguyen HH, Ranasinha S, Vollenhoven B. Increased detection of co-morbidities with evaluation at a dedicated adult Turner syndrome clinic. Climacteric. 2017; 20: 442–447.
[27] Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, *et al*. Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations. The Journal of Clinical Endocrinology and Metabolism. 2018; 103: 1790–1803.
[28] Fiot E, Alauze B, Donadille B, Samara-Boustani D, Houang M, De Filippo G, *et al*. Turner syndrome: French National Diagnosis and Care Protocol (NDCP; National Diagnosis and Care Protocol). Orphanet Journal of Rare Diseases. 2022; 17: 261.
[29] Cameron- Pimblett A, La Rosa C, King TFJ, Davies MC, Conway GS. The Turner syndrome life course project: Karyotype-phenotype analyses across the lifespan. Clinical Endocrinology. 2017; 87: 532–538.
[30] Bakalov VK, Cheng C, Zhou J, Bondy CA. X-Chromosome Gene Dosage and the Risk of Diabetes in Turner Syndrome. The Journal of Clinical Endocrinology and Metabolism. 2009; 94: 3289–3296.
[31] Livadas S, Xekouki P, Fouka F, Kanaka-Gantenbein C, Kaloumenou I, Mavrou A, *et al*. Prevalence of Thyroid Dysfunction in Turner's Syndrome: a Long-Term Follow-up Study and Brief Literature Review. Thyroid. 2005; 15: 1061–1066.
[32] Yeşilkaya E, Bereket A, Darendeliler F, Baş F, Poyrazoğlu Ş, Küçükemre Aydın B, *et al*. Turner syndrome and associated problems in Turkish children: a multicenter study. Journal of Clinical Research in Pediatric Endocrinology. 2015; 7: 27–36.
[33] Chou Y, Wang C, Lin C, Chung H, Lo F. Association between cardiovascular anomalies and karyotypes in Turner syndrome patients in Taiwan: a local cohort study. Pediatrics and Neonatology. 2020; 61: 188–194.
[34] Fuchs MM, Attenhofer Jost C, Babovic-Vuksanovic D, Connolly HM, Egbe A. Long-Term Outcomes in Patients with Turner Syndrome: a 68-Year Follow-up. Journal of the American Heart Association. 2019; 8: e011501.
[35] Stefil M, Kotalczyk A, Blair JC, Lip GYH. Cardiovascular considerations in management of patients with Turner syndrome. Trends in Cardiovascular Medicine. 2021. (in press)
[36] Los E, Quezada E, Chen Z, Lapidus J, Silberbach M. Pilot Study of Blood Pressure in Girls with Turner Syndrome: An Awareness Gap, Clinical Associations, and New Hypotheses. Hypertension. 2016; 68: 133–136.
[37] De Groote K, Demulier L, De Backer J, De Wolf D, De Schepper J, T'sjoen G, *et al*. Arterial hypertension in Turner syndrome: a review of the literature and a practical approach for diagnosis and treatment. Journal of Hypertension. 2015; 33: 1342–1351.
[38] Silberbach M, Roos-Hesselink JW, Andersen NH, Braverman AC, Brown N, Collins RT, *et al*. Cardiovascular Health in Turner Syndrome: a Scientific Statement from the American Heart Association. Circulation: Genomic and Precision Medicine. 2018; 11: e000048.
[39] Trolle C, Mortensen KH, Hjerrild BE, Cleemann L, Gravholt CH. Clinical care of adult Turner syndrome–new aspects. Pediatric Endocrinology Reviews. 2012; 9: 739–749.