Original Article

Delayed Presentation of Turner Syndrome: Challenge to Optimal Management

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Abstract

Background: Turner syndrome (TS) is a chromosomal disorder associated with dysmorphic features and comorbidities, with recent trends focusing on early diagnosis for adequate management. **Aim:** The aim is to study the age and mode of presentation of TS, associated comorbidities and look for any correlation with the genotype. **Material and Methods:** This was a retrospective analysis of girls with TS attending the endocrinology clinic of a tertiary care center. Their age, mode of presentation, and clinical features were noted. All participants underwent ear examination, echocardiography, and ultrasonography of the abdomen. Laboratory investigations included serum T4, thyroid-stimulating hormone, thyroid peroxidase antibodies, follicle-stimulating hormone, fasting, and 2-h plasma glucose after 75 g glucose load and a karyotype. Simple descriptive statistical methods were used. **Results:** Seventeen cases of TS were seen with a median age of presentation of 18 years (range 14–42 years). Primary amenorrhea was the most common reason for seeking medical attention (76.4%) followed by short stature and diabetes mellitus (11.8% each). The mean height at presentation was 137.5 ± 5.4 cm. Monosomy of X chromosome (45,X) was the most common karyotype obtained in 58.8% of the patients, followed by 45,X/46, XX in 17.6%, 45,X/46X,i(X)(q10) in 11.8%, and 45,X/47,XXX and 46X,delXp11.2 in 5.9% patients each. Bicuspid aortic valve was seen in two patients having a 45,X/46,XX karyotype. **Conclusion:** Primary amenorrhea is the most common presenting feature in girls with TS leading to a delayed age of presentation. Short stature and dysmorphic features are often overlooked in infancy and childhood due to socioeconomic factors. This late age of presentation is a cause of concern as early detection and management is important for height outcomes, bone health, and psychosocial support. Assessment of comorbidities becomes important in this setting.

Keywords: *Bicuspid aortic valve, diabetes mellitus, karyotype, primary amenorrhea*

Introduction

Turner syndrome (TS) first described by Henry Turner and Otto Ulrich in the 1930s is a congenital disorder characterized by a distinct clinical phenotype associated with a complete or a partial loss of the second sex chromosome in at least a proportion of the body's cells in individuals with a female phenotype.[1] Care of a patient with TS focuses on optimizing growth, achieving sexual maturation, detecting associated congenital anomalies, especially cardiac defects to prevent a fatal event, assisting in fertility, and addressing long-term health issues including psychosocial problems. However, despite significant advances in diagnosis and management of this condition, barriers to achievement

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of these goals are often seen due to lack of awareness of the problem, late presentation, and financial constraints. We present here the clinical picture and karyotype of patients with TS presenting to an endocrinology clinic in a tertiary care center.

Material and Methods

The present study is a retrospective analysis of patients with TS who were seeking medical attention for the first time and had presented to the endocrinology clinic of a tertiary care center between January 2012 and July 2017. The age of presentation, presenting complaints and detailed clinical examination including height, presence of any typical Turner stigmata, skeletal anomalies, and Tanner staging were noted. Height standard deviation score (SDS) was calculated using recently published standards.[2] Fasting and 2-h postglucose loading plasma glucose were estimated using glucose oxidase method using Vitros 5600 autoanalyzer. T4, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and thyroid peroxidase (TPO) antibodies were measured by chemiluminescence immunoassay on IMMULITE 1000 using commercial kits (normal values: TSH, 0.4–4.0 mIU/L; T4, 57.9–161 nmol/L; FSH, 2.8–11.3 mIU/mL; TPO antibody, 0–150 IU/dL). The intra-assay coefficient of variation (CV) was 4.5% and inter-assay CV was 8% for T4. The intra- and inter-assay CV of the test for FSH was 4.2% and 4.6%, respectively. The intra- and inter-assay CV was 4.3% and 10.5%, respectively, for TPO antibody.

All patients underwent an ultrasonography (USG) of the abdomen and pelvis, for evaluation of mullerian structures and gonads and to rule out any renal anomalies. Patients also had an echocardiographic evaluation for cardiac defects and a detailed ear examination. Karyotype was obtained by chromosomal analysis using peripheral blood lymphocyte culture, on the basis of GTG-banding technique with 500-band resolution.

Simple descriptive statistical methods were used for analyzing data and percentages were calculated wherever appropriate.

Results

A total of 17 cases of TS were included in this study. Baseline characteristics of the patients are depicted in Table 1. The mean age of the participants at presentation was 19.4 ± 6.5 years with the median age being 18 years (range 14–42 years). The most common presenting complaints were primary amenorrhea, short stature, and diabetes mellitus. Two patients, who presented at the age of 42 years and 25 years, were seeking treatment for diabetes mellitus and were never evaluated for TS despite classical features. Spontaneous menarche was reported by 1 (5.9%) patient, following which she developed oligomenorrhea and later on secondary amenorrhea. The mean height of the patients was 137.5 ± 5.4 cm with mean height SDS of − 3.04 ± 0.86 (range: −4.8–−1.8).

Table 1: Baseline characteristics of the Turner syndrome patients

Parameter	Value
Age at presentation (years), mean±SD (range)	19.4±6.5 (14-42)
Height at presentation (cm), mean±SD	137.5±5.4
Height SDS at presentation, mean±SD (range)	−3.04±0.86 (−1.8-−4.8)
Presenting complaint (%)	
Primary amenorrhea	76.5
Short stature	11.8
Diabetes mellitus	11.8

SD=Standard deviation, SDS=Standard deviation score

Clinical features of the patients included in the study are presented in Table 2. Webbing of the neck was present in 47.1% (eight patients) while low hairline was noted in 70.6% (12 patients) and multiple nevi in 76.5% (13 patients) of cases. Cubitus valgus was the most common skeletal anomaly observed in 76.5% of the patients, followed by short neck in 58.8%, short 4th and/or 5th metacarpal in 52.9%, high-arched palate in 52.9%, and pectus excavatum and clinodactyly in 17.6% each. In addition, scoliosis was noticed in three patients (17.6%) while one patient (5.9%) had micrognathia.

Most (88.2%) of the patients had no pubertal development (Tanner stage 1) while 2 (11.8%) had some pubertal development (Tanner stage 2 and 3 in 1 patient each). Three patients (17.6%) were found to have type 2 diabetes mellitus of whom it was the presenting complaint in two of them. One patient was diagnosed to have impaired fasting glucose on evaluation. Of the 3 diabetic patients, 2 patients had normal body mass index while 1 was overweight, and all of them were controlled on oral hypoglycemic agents. Dyslipidemia was a feature in all three of them while hypertension needing therapy was present in two patients aged 25 years and 42 years. One patient was found to have overt hypothyroidism while 1 was detected to have subclinical hypothyroidism. TPO antibodies were detected in 3 (17.6%) patients.

The various karyotypes obtained in the TS cases are shown in Table 3. Monosomy of X chromosome (45,X) was the most common karyotype obtained in 58.8% of the patients while 17.6% patients had 45,X/46,XX mosaic karyotype. 45,X/46X,i(X)(q10)

Table 2: Clinical features of the Turner syndrome patients

Clinical feature	Monosomy X (*n*=10)	Other karyotypes (*n*=7)	Total (*n*=17)
Primary amenorrhea	9 (90)	7 (100)	16 (94.1)
Secondary amenorrhea	1 (10)	0	1 (5.9)
Non/poor development of secondary sexual characteristics	10 (100)	7 (100)	17 (100)
Short neck	7 (70)	3 (42.9)	10 (58.8)
Webbing of neck	5 (50)	3 (42.9)	8 (47.1)
Low hairline	9 (90)	3 (42.9)	12 (70.6)
Cubitus valgus	9 (90)	4 (57.1)	13 (76.5)
Short 4th and/or 5th metacarpal	5 (50)	4 (57.1)	9 (52.9)
Spine deformity	2 (20)	1 (14.3)	3 (17.6)
High-arched palate	6 (60)	3 (42.9)	9 (52.9)
Pectus excavatum	3 (30)	0	3 (17.6)
Clinodactyly	2 (20)	1 (14.3)	3 (17.6)
Multiple nevi	8 (80)	5 (71.4)	13 (76.5)
Micrognathia	0	1 (14.3)	1 (5.9)
Hypertension	2 (20)	0	2 (11.8)
Diabetes mellitus	2 (20)	1 (14.3)	3 (17.6)
Prediabetes	1 (10)	0	1 (5.9)
Overt hypothyroidism	1 (10)	0	1 (5.9)
Subclinical hypothyroidism	1 (10)	0	1 (5.9)
Cardiac abnormalities (on echocardiography)	1 (10)	2 (28.6)	3 (17.6)

Table 3: Karyotypes obtained in Turner syndrome patients

Karyotype	Number of patients (%)
45,X	10 (58.8)
45,X/46, XX	3 (17.6)
45,X/46, X, i (X) (q10)	2 (11.8)
45,X/47, XXX	1 (5.9)
46X, delXp11.2	1 (5.9)

karyotype was detected in 2 (11.8%) patients while 45,X/47,XXX and 46X,delXp11.2 karyotypes were found in 1 (5.9%) patient each.

FSH levels ranged from 43.1 mIU/mL to 170 mIU/mL, with mean levels being 102.5 ± 43.8 mIU/mL. On USG, 82.4% patients had hypoplastic uterus whereas rudimentary uterus was noted in 17.6% patients. Ovaries could not be visualized in 58.8% of the cases, whereas 35.3% cases had bilateral streak ovaries and 1 (5.9%) patient was found to have unilateral streak ovary with nonvisualization of ovary on the other side. No structural renal anomalies were detected in any of the patients. Echocardiography revealed abnormalities in 3 (17.6%) patients, with two patients having bicuspid aortic valves and one patient had mild dilatation of the right atrium and ventricle. Hearing assessment did not reveal any abnormality in any of the cases. Behavioral abnormalities were not reported by the patients or their parents. School performance was poor in 4 (23.5%) patients, leading to drop out before class 10 while it was average in the rest.

All patients were started on oral estrogen (ethinylestradiol or conjugated equine estrogen) for induction of sexual maturation followed by cyclical estrogen-progestogen therapy once breakthrough bleeding occurred or after 1 year of initiation of estrogen therapy. None of the patients received growth hormone both because of late age of presentation and financial issues.

Discussion

Of the 17 patients with TS, the median age at diagnosis was 18 years with a range of 14–42 years. This is in stark contrast to a Belgian study of 242 girls where the median age of diagnosis was 6.6 years and ranged from prenatal life to 18.3 years.[3] In this study, patients with a 45,X karyotype were more frequently diagnosed before 1 year of age, while after the age of 1 year, the median age at diagnosis was 10.1 years, with no difference between different karyotypes. Another recent study reported a mean age of diagnosis of 5.9 ± 5.3 years with a range of prenatal to 17.9 years among 67 girls with TS.[4] Indian data, however, show a great delay in diagnosis. In a study from eastern India, the mean age at diagnosis was 11.7 ± 5.2 years with a range of 2–23 years.[5] This late age of diagnosis as in our study precludes meaningful interventions in optimizing growth potential like GH therapy. When TS is detected and managed early enough, psychological and educational support can help with academic achievement and social integration. Early initiation of estrogen therapy also aids in bone integrity and socialization.[6]

Type 2 diabetes mellitus was seen in 3 (17.6%) of our patients associated with dyslipidemia in all and hypertension in one of them [Table 4]. A recent study in 113 Italian TS patients concluded that diabetes is frequent in TS and is specific to the syndrome.[7] The risk of type 2 diabetes is increased about four folds in patients with TS across all age groups in epidemiological studies.[8] Various abnormalities in glucose homeostasis have been described including hyperinsulinemia, insulin resistance, and decreased insulin secretion.[9,10] This has prompted the recent guideline of lifelong annual measurement of HbA1c with or without fasting plasma glucose starting at the age of 10 years.[8] As diabetes was the reason for seeking medical attention in two of our patients aged 25 and 42 years rather than short height or primary amenorrhea, associated comorbidities may assume more importance in certain socioeconomic settings.

Hypothyroidism was noted in two patients and TPO antibodies were positive in three. Screening for hypothyroidism is recommended at diagnosis and yearly thereafter.[8] Girls with TS are predisposed to the development of various autoimmune disorders of which hypothyroidism is the most common. This may be detected in childhood and its prevalence increases with age.[11] Although the exact mechanism is not known, there is a decrease in CD4:CD8 lymphocyte ratio suggesting an immune change predisposing to autoimmunity.[12]

A 45,X karyotype was the most common cytogenetic abnormality seen in 58.8% of our patients. Monosomy of X chromosome has been the most commonly reported karyotype in TS, ranging from 38.9% to 50.7%.[3,5,7,13] None of our patients had a Y cell line. Because of the small number of patients involved, it is difficult to make a karyotype-phenotype correlation. A 45,X/47,XXX has been reported to be associated with a milder phenotype and a higher probability of menstruation also reported in mosaic cell lines.[14] However, our single patient with the above karyotype presented at 15 years with sexual infantilism and short stature of − 2.3 SDS. Hypothyroidism has also been reported to be more frequent in karyotypes other than 45,X.[15] This was, however, not seen in the present study where both patients had a 45,X karyotype [Table 4]. In the same series, cardiac defects were reported to be most common with monosomal karyotype followed by isochromosome Xq.[15] However, in our series, bicuspid aortic valves were detected in two patients who had a 45,X/46,XX karyotype [Table 4]. Bicuspid aortic valves have also been reported in 28.6% of participants with Xp deletions and coarctation of the aorta in 6.7%.[16] However, our single patient with an Xp deletion did not have any cardiac defects. Patients with isochromosome Xq have been found to be significantly heavier than those with other karyotype groups which was not seen in the present study.[13] Tanner stage 3 was seen in only one patient in our study who had a 45,X/46,XX karyotype.

All our patients received oral estrogen therapy for induction of secondary sexual characters. As all our patients were 14 years or older induction of menarche was important for psychological reasons, and hence, a progestin was added after a year. Current recommendations stress on induction of puberty at 11–12 years of age.[8] However, this was not possible in our series due to late presentation. Delay in estrogen commencement is reported to be an independent risk factor for the lower bone density observed in women with TS emphasizing the need for early pubertal induction.[17]

Conclusion

Primary amenorrhea is the most common presenting feature in girls with TS leading to a delayed age of presentation. Short stature and dysmorphic features are often overlooked in infancy and childhood due to socioeconomic factors. This late age of presentation is a cause for concern as therapy for improving height outcomes is often not possible, and delay in estrogen therapy has detrimental effect on bone health and social and psychological well-being. Hence, quick induction of puberty and assessment for comorbidities becomes the prime issue in our scenario unlike the developed countries where diagnosis is relatively early and focuses on optimizing growth, detecting congenital anomalies, and diagnosing and tackling psychosocial problems.

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Table 4: Comorbidities and their associations in Turner syndrome patients

Comorbid condition	Mean age	Mean BMI	Hypertension (%)	Karyotypes	Tanner stage
Diabetes mellitus (*n*=3)	28.3	22.8	2 (66.7)	45,X (*n*=2)	Tanner 1 (*n*=2)
				45,X/46, XX (*n*=1)	Tanner 3 (*n*=1)
Hypothyroidism (*n*=2)	31.5	17.8	1 (33.3)	45,X	Tanner 1
Bicuspid aortic valve (*n*=2)	21.5	17.4	0	45,X/46, XX	Tanner 1

BMI=Body mass index

Conflicts of interest

There are no conflicts of interest.

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