Turner Syndrome Genotype and phenotype and their effect on presenting features and timing of Diagnosis

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Abstract

Background

Turner syndrome (TS) is a common genetic disorder caused by abnormalities of the X chromosome. We aimed to describe the phenotypic characteristics of TS patients and evaluate their association with presenting clinical characteristics and time at diagnosis.

Methods

We studied females diagnosed with TS at King Abdul Aziz Medical City (KAMC), Riyadh between 1983 and 2010. Patients were classified based upon karyotype into females with classical monosomy 45,X (group A) and females with other X chromosome abnormalities (mosaic 45,X/46,XX, Xqisochromosomes, Xp or Xq deletion) (group B). Clinical features of the two groups were analyzed.

Results

Of the 52 patients included in the study, 16(30.8%) were diagnosed with classical monosomy 45,X and the rest with other X chromosome abnormalities. Only 19(36.5%) patients were diagnosed in infancy and the remaining during childhood or later (odds ratio (OR) = 4.5,95%CI 1.27-15.90, p=0.02). Short stature was universal in group A versus 77.8% in group B. All patients in group A had primary amenorrhea compared with 63.2% of those in group B (P = 0.04); the rest of group B had secondary amenorrhea. Cardiovascular abnormalities were higher in group A (OR=3.50, 95%CI 0.99-12.29, p-value =0.05). Renal defects and recurrent otitis media were similar in both groups.

Conclusion

This study suggests that karyotype variations might affect the phenotype of TS; however, it may not reliably predict the clinical presentation. Chromosomal analysis for all suspected cases of TS should be promptly done at childhood in order to design an appropriate management plan early in life.

Keywords: Turner Syndrome, phenotype, genotype, Saudi Arabia

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Introduction

Turner syndrome (TS) is one of the most common genetic disorders; occurs with an incidence of I: 2,500 female live births. [1] It results from complete or partial chromosome X monosomy. [2]

TS is associated with abnormalities of the X chromosome and characteristic clinical features of short stature, gonadal dysgenesis, sexual developmental deficiencies, cardiac and/or renal defects, webbed neck, low-set ears, skeletal deformities including cubitus valgus, a propensity to ear infections and hearing deficits.[3]

The diagnosis of TS requires the presence of characteristic physical features in phenotypic females coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism. [1, 2]

Many of affected females are diagnosed at birth, especially those with a 45,X karyotype, due to the presence of dysmorphic features or cardiac abnormalities. However, in many instances the diagnosis of TS may be delayed until childhood, adolescence or, unfortunately, until adulthood, when evaluation for short stature, pubertal delay, amenorrhea and infertility yields the diagnosis. [4] Early diagnosis is an important aspect of ideal treatment for the patient with TS.

Despite short stature, which seems to be the general clinical characteristic of TS, all other clinical stigmata are inconsistent, even in individuals with non-mosaic 45,X. Possible explanation for this fact is that the physical manifestations of TS largely depends on the karyotype. [5] Parental origin of the X chromosome also can contribute to their phenotypes. [6] In approximately two thirds of women with TS, the normal X chromosome is maternal in origin. [7] Patients with mosaic 46,XX karyotype or isochromosome Xq results in milder phenotype, [5, 6, 8] while patients with mosaicism for 46,XY cell line or structural rearrangement of the Y chromosome mostly have masculinized external genitalia and are at increased risk for having gonadoblastoma and other gonadal tumors. [5, 9]

This study describes the genotypic and phenotypic characteristics of TS patients, who were followed up in our hospital, and aims to correlate their phenotype with the genotype.

Methods

This study is a retrospective, observational study of Saudi females (aged from birth to 39 years) with karyotype-proven TS diagnosed and managed at King Abdul Aziz Medical City Hospital (KAMC) between 1983 and 2010.

Subjects of this study were drawn from all cases whose cytogenetic results contained monosomy X and/or mosaic cell population with variant sex chromosome abnormalities.

Chromosomal analysis was performed on the basis of G-banding technique at high resolution.

Data were collected by reviewing the medical records of all identified patients, and included age at diagnosis, detailed clinical features, chromosomal analysis, and occurrence of complications. We define obese TS females in our sample as all adult females with BMI > 30. We determined the variations of sex chromosomes abnormalities in TS individuals and the different clinical features at the age of diagnosis for karyotype-phenotype correlations.

Data were reported as proportions and were analyzed using the χ^2 test (or Yates' corrected χ^2test). In addition, a logistic regression analysis was performed to determine the clinical features and comorbid conditions significantly associated with the likelihood of the monozomy (45x) abnormality, modeling patients with mosaic or other chromosome x abnormalities as a baseline risk group. All tests were two-sided and a p-value <0.05 was considered significant. SPSS ver. 19 was used to analyze data.

Results

We classified the 52 TS patients into Group A and Group B according to their chromosomal analysis results. Thirty one percent of our patients had classical monosomy 45,X, (Group A), while the rest (Group B) showed other X chromosome abnormalities (Isochromosome Xq, mosaic karyotype 45,X/46,XX, ring X chromosome, Deletions Xp and other structural abnormality of Y chromosome), of which two thirds had isochromosomes of the long arm of X chromosome. Detailed description of patients karyotype is shown in Table 1.

Table 1: Classifications of chromosomal abnormalities

karyotype classification	n(%)	Karyotype
Group A		
Standard monosomy	16(31)	45,X
Group B		
IsochromosomeXq	16(31)	46,X,i(X)(q10); psu idic(X)(p11.2),46,X,i(X)(q10)[16]/45,X[7]/46,X,r(?)[6]/47,X,i(X)(q10)x2[2];
X Mosaicism	7(13)	45X/46XX
Ring	3(6)	46,X,r(X)/45XO; 45,X[14]/46,X,r(X)(p11.2q24)[6];
structural abnormality of Y chromosome	3(6)	idic(Y)
Deletions Xp	1(2)	46,X,del(X)(P11.1)
Y Mosaicism	1(2)	46,XY[32]/45,X[18]
Others	5(9)	46,X,der(X)(pter->q21::p11.2->pter); 46,X,del(X)(q27); 45,X,t(4;7)(q25;q31.2); 45,X/46,X,psr

The median (IQR) age of diagnosis in the classical monosomy group A was 1 (1-102) month while for group in was 96 (49.5-198) months. We found only 17/52 patients (32.7%) were diagnosed during infancy while the majority of our cases were referred for chromosomal evaluation during childhood or later [odds ratio (OR) = 4.5, 95% confidence interval (CI) 1.27-15.90, Wald test p-value =0.02). Nine (17%) cases were diagnosed late during adulthood of which one third had 45,X and the rest were from group B. The age of diagnosis of each group was studied and presented in Table 2.

Table 2: Distribution of age at diagnosis of chromosome analysis

Age	Group A n=16 n(%)	Group B n=36 n(%)
0-11 Months	9 (56.3)	8(22.2)
1-12 Years	4(25)	16(44.4)
13-18 Years	0	6(16.7)
≥18	3(18.7)	6(16.7)

χ^2test p-value = 0.052

Patients with 45, X had more severe clinical features than those with other forms of karyotypes abnormalities. Short stature was universal in the classical monosomy group (100%), compared with 77.8% of the second group (Yates' corrected χ^2 test P=0.10). Cardiac anomalies (OR=3.50, 95%CI 0.99-12.29, p-value =0.051), short neck (OR=3.34, 95%CI 0.98-11.4, p-value =0.054) as well as lymphedema of hands and feet (OR=6.60, 95%CI 1.39-31.28, p-value =0.02) were significantly more common in 45,X patients. In contrast hypothyroidism (OR=0.60, 95%CI 0.14-2.56, p-value =0.49) and obesity (Yates' corrected χ^2 test P=0.29) were more common in patients with other chromosome X abnormalities. Occurrence of renal defects (OR=0.89, 95%CI 0.15-5.13, p-value =0.89) and ear problems (OR=1.25, 95%CI 0.38-4.07, p-value =0.71) were almost similar in both groups. The summary of their clinical features are presented in Table 3.

Table 3: Frequency of Turner major clinical features and co-morbidities in relation to different karyotypes (Group A n=16, Group B n=36)

Clinical feature	Group A	Group B	OR(95%CI)	P value
	n(%)	n(%)		
Diagnosed at infancy				
Yes	9(56.3)	8(22.2)	4.5(1.27-15.90)	**0.02**
No	7(43.8)	28(77.8)	1	
Short stature				
Yes	16(100)	28(77.8)	Incalculable	
No	0	8(22.2)		
CVS abnormalities				**0.051**
Yes	8(50)	8(22.2)	3.50(0.99-12.29)	
No	8(50)	28(77.8)	1	
Renal abnormalities				**0.89**
Yes	2(12.5)	5(13.9)	0.89(0.15-5.13)	
No	14(87.5)	31(86.1)	1	
Short neck				**0.054**
Yes	9(56.3)	10(27.8)	3.34(0.98-11.4)	
No	7(43.8)	26(72.2)	1	
Lymphedema				**0.02**
Yes	6(37.5)	3(8.3)	6.60(1.39-31.28)	
No	10(62.5)	33(91.7)	1	
Hypothyroidism				**0.49**
Yes	3(18.8)	10(27.8)	0.60(0.14-2.56)	
No	13(81.3)	26(72.2)	1	
Eye abnormalities				**0.12**
Yes	4(25.0)	3(8.3)	3.68(0.71-18.83)	
No	12(75)	33(91.7)	1	
Ears abnormalities				**0.71**

Yes	8(50)	16(44.4)	1.25(0.38-4.07)
No	8(50)	20(55.6)	
Obesity			
Yes	0	5(13.9)	Incalculable
No	16(100)	31(86.1)	
Amenorrhea*			
- Primary	8(100)	12(63.2)	Incalculable
- Secondary	0	7(36.8)	

Group A: Monosomy: 45,X;Group B: mosaic or other chromosome X abnormalities

OR: odds ratio, 95%CI: 95% confidence interval. P-value: Wald test.

*Amenorrhea: based on 8 patients in Group A and 19 in Group B older than 12 years of age

Cardiovascular (CVS) anomalies were present in one third of the patients; divided equally between the two groups, almost all were diagnosed with TS during infancy. In group B patients with CVS anomalies 75% had isochromosome Xq. The cardiovascular defects were coarctation of aorta (37.5%), bicuspid aortic valve (31.2%), while the rest had ventricular septic defect, patent ductus arteriosus, hypoplastic left ventricle and hypertension.

Renal structural anomalies were found in 7 (13.4%) patients, all were diagnosed during infancy. Horseshoe kidney was the main renal defect followed by vesico-uretral reflux and solitary kidney.

Amenorrhea was present in all TS patients older than 12 years (27 patients), of which almost one third had 45,X karyotype and the remaining had other karyotype abnormality. All 45,X patients with amenorrhea had primary amenorrhea, while one third of group B (28% with ring X chromosome) had spontaneous menarche with subsequent secondary amenorrhea (P=0.04).

The main ear problems were hearing defects and chronic otitis media, while majority of the eye problems were strabismus and hyperopia.

Discussion

TS is characterized by the presence of an abnormal X chromosome, in the form of monosomy, mosaicism of a 45X cell line with another cell line, which might be 46XX, 46XY or an abnormal sex chromosome rearrangement. There is a correlation between the exact cytogenetic appearance and the phenotype in TS. [5, 6] Pure 45,Xmonosomy is the most common karyotype and is associated with the most abnormal phenotype.

Although clinical features of TS have been well defined, the severity of phenotype in TS individuals varies according to the underlying chromosomal constitution.[5] In this study, we assessed the association between karyotype and phenotype. In our series, a third of cases had monosomy X chromosome and almost the rest had other X chromosomal anomalies, of which two thirds had isochromosomes of the long arm of X chromosome. This variability in the karyotypes assumed to contribute to the phenotypes diversity found.

In terms of age of diagnosis, for most of our TS cases, the awareness of clinicians or the parents increased after appearance of significant clinical signs, such as short stature, primary amenorrhea, lack of secondary pubertal signs. Cases diagnosed during infancy mostly had more obvious clinical features such as dysmorphism, lymphedema, congenital cardiac and renal anomalies that might had alerted the physicians earlier for the need of prompt diagnosis and management.

In this cohort, all TS patients have short stature. Although short stature is the cardinal feature of this disorder however the severity of these problems varies considerably among individuals according to their karyotype. [10, 11] This observation revealed that short stature was universal in monosomy patients versus one fourth of those with other X chromosome abnormality having near normal stature. The cause of short stature in TS is thought to be due to a primary bone defect or to loss of SHOX gene responsible for growth, which lies

in the pseudoautosomal region of X chromosome. [12] Growth hormone treatment started in early childhood in TS patients may improve the final adult height. [12]

Ovarian failure with subsequent estrogen deficiency is a hallmark of TS. Although approximately 30% of girls with TS have evidence of some spontaneous pubertal changes, many of these girls will not progress fully through puberty and only 16% will have spontaneous menses with eventually secondary amenorrhea.[12] Menses are more likely to occur in girls who are mosaics or have ring X chromosomerather than those with a 45X karyotype. Thus long-term estrogen replacement therapy is the cornerstone in management of TS patients.

The most serious, life-threatening consequences of X-chromosome haploinsufficiency involve the cardiovascular system. This is most apparent during fetal development, where major cardiac defects result in high mortality for fetuses with a 45,X karyotype. [13-15] Structural cardiac anomalies are most prevalent in TS with pure 45,X monosomy. [16] The most common malformation found is coarctation of the aorta, which may be preductal or postductal. [17] In our series, most TS patients with cardiac defects have monosomy karyotype followed by isochromosome Xq.

Hearing problems and ear malformations are common in TS and correlate with karyotype. It was found that sensorineural hearing loss and occurrence of auricular anomalies were significantly increased in 45,X patients [18, 19] and this is consistent with our findings.

Structural malformations of the kidney occur more frequently in 45,X patients, whereas collecting-system malformations occur more frequently in those with mosaic/structural X karyotypes. [20, 21] In our study, renal anomalies were almost similar in both groups, mainly horseshoe kidney. Vesico-uretral reflux grade III was found in one patient with isochromosome X, while the remaining had other structural kidney anomalies. It is recommended that all girls with TS should have a renal ultrasound study performed at diagnosis.

The incidence of autoimmune thyroid disease in females with TS increases with age. Previous studies demonstrated a doubling in the prevalence of autoimmune thyroid disease from the first to the third decade of life being particularly prevalent in women with the isochromosome karyotype compared with other karyotypes. [22, 23] Thus hypothyroidism is more likely to be diagnosed in adults with TS. Our results confirm this with 46.6% of females having hypothyroidism of which 18.8% with 45,X compared with 27.8% of females with other karyotypes, half of them had isohromosomeXq.

The cause of obesity in females with TS is unknown, but may be related, in part, to estrogen deficiency. One study showed that women with TS had reduced physical fitness which is partially improved by sex hormone replacement. [24] Our study showed that obesity was more prevalent in TS patients with mosaic/other X chromosome abnormalities who had primary amenorrhea while it was not found in monosomy patients. This might be explained by the late diagnosis of non monosomy patients during adulthood while most of our monosomy patients were diagnosed earlier at younger age.

All of the above mentioned findings strongly suggest that mosaic TS is more compatible with life rather than the non mosaic monosomy form. Our results are in agreement with the study of Held et al. demonstrating that mosaic condition is more pronounced than the 45,X. [25]

In terms of TS management, especially for growth hormone treatment, these data had clinical importance, because growth response is negatively correlated with age at the start of therapy. [26, 27] Growth failure in TS typically manifest in early childhood and can be identified by careful auxological assessment and charting with keeping high index of suspicion for TS diagnosis in any female with short stature. Proper treatment of the patient with TS should begin with establishment of the correct diagnosis at the earliest possible age.

Our study has some limitations. First, it was a retrospective study with data collection relied upon reviewing the medical records with the possibility of missing data and loss from follow up. Second, it was conducted in one center that might not represent other health care centers in Saudi Arabia. However, our hospital is a tertiary care center in Riyadh, the capital of Saudi Arabia.

Conclusion

The results of this study suggest that karyotype variations might affect the phenotype of TS. Therefore, chromosomal investigation for all suspected cases of TS should be done as early as possible in order to design an appropriate management plan early in life. It is important to study karyotype-phenotype correlations in patients with Turner syndrome to obtain further information about the effect of different X chromosome abnormalities on the severity of clinical features.

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